ANNUAL REPORTS

OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

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PREFACE

The present volume includes reports of the work of the past year, which has been carried out on the same lines as in previous years. The scope of this work is described in the preface of Volume II.

In addition to the work growing out of the investigations by the Council, the Laboratory's work includes the constant examination of "patent medicines" and a large amount of investigation of chemical questions connected with the Propaganda and the Queries and Minor Notes departments of THE JOURNAL of the American Medical Association.

In conformity with previous reports, the volume contains an account of those portions of the laboratory's activities which it was thought would be of interest to drug analysts, i. e., those engaged in the examination of medicines.

CONTENTS

PART I

REPRINTS OF CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION

THE WORK OF THE AMERICAN MEDICAL ASSOCIATION CHEMICAL LABORATORY*

W. A. Puckner, Phar.D.

(*Reprinted from The Journal A. M. A., Nov. 25, 1916, p. 1593*)

The American Medical Association Chemical Laboratory was established nearly ten years ago — in the fall of 1906. The reason for its existence was primarily the fact that the Council on Pharmacy and Chemistry found it difficult to secure from outside sources such help as it needed in checking up the composition and properties of proprietary medicines under investigation. Medical schools and similar institutions were found ready to lend their assistance in pharmacologic and medical investigations; but the chemical investigation required the establishment of a laboratory under the control of the American Medical Association.

As years have passed, the scope of the laboratory has been extended: Its services have been requisitioned by THE JOURNAL in various ways. Thus, when requested, the laboratory reviews and verifies the chemical data contained in editorials and original contributions. The laboratory is often called on for information as to the character and composition of quack treatments and so-called "patent medicines." Through the columns of THE JOURNAL and through direct corre-

* Read before the Section on Pharmacology and Therapeutics at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

spondence, the laboratory responds to requests of physicians with information regarding the composition of medicines which they prescribe or in which they are interested. The laboratory attempts to be to the members of the American Medical Association what the prescription pharmacist is, or should be, to the prescribing physician — a storehouse of chemical and pharmaceutical information. In the belief that an insufficient familiarity with the chemistry and pharmacy of drugs constitutes the chief reason for the extensive use of unscientific, worthless or fraudulent proprietary remedies, this service is rendered by the laboratory as a contribution to the cause of rational therapy.

Since the efficiency of the American Medical Association Chemical Laboratory will increase as its activities are better known, the following more detailed statement of its work is offered:

THE LABORATORY AND THE COUNCIL

As stated in the rules of the Council on Pharmacy and Chemistry, it is "manifestly impossible for the Council to investigate the composition of every complex pharmaceutical mixture . . . "; "it can only give an unbiased judgment on the available evidence." In line with this, the laboratory does not undertake to prove the composition or constitution of all new synthetics, nor does it attempt to determine the individual composition of proprietary mixtures. It checks all claims that seem doubtful, however, and uses its best endeavors to secure correction of misstatements with regard to proprietary remedies and improvement in the quality of these products. Further, it reexamines, when this seems desirable, the products which have been admitted by the Council to New and Nonofficial Remedies, and thus determines, from time to time, their dependability. The fact that no product admitted to New and Nonofficial Remedies has later been shown to be untrue to its claimed composition is, it is believed, an indication that in this respect the laboratory has

succeeded in performing the work for which it was primarily created.

In this connection the question may be asked, Are many proprietary medicines exploited to the medical profession with false claims in regard to their composition? Also it may be asked, Has the number of proprietaries marketed with false statements of composition decreased since the Council and the laboratory began their work? Answering the latter question first: There is no doubt that today fewer proprietary medicines are being sold with false claims as to composition than there were ten years ago. When the Council began its work, medical journal advertising teemed with statements regarding the composition of medicines which any chemist familiar with medicines would not hesitate at sight to brand as untrue. Today such manifestly false claims are rare. Coming to the former question: Many false statements regarding the identity and composition of remedies have been made in ignorance. This is not surprising when it is remembered that the most ignorant may and do engage in the manufacture of medicines. Besides ignorance, however, an accommodating conscience on the part of the manufacturer and a failure on the part of the medical profession to appreciate the danger which lies in the use of medicines of unknown composition unquestionably have greatly encouraged the marketing of falsely declared medicines. A glaring illustration of the ignorance of manufacturers — for it is hard to believe that any business concern would deliberately court prosecution by the federal authorities through false statements on labels — is the fact that nearly thirty years ago A. B. Lyons published a report[1] pointing out that the proprietary Iodia was falsely declared as to composition and that in 1914 when the Council examined this preparation such incorrect declaration appeared on the label.[2] That many physicians do not recognize the danger to their patients and their repu-

1. Lyons, A. B.: Detroit Lancet, 1882, **6**, 157.
2. The Journal A. M. A., Nov. 21, 1914, p. 1871.

tation in the use of medicines, the composition of which they do not know, is illustrated by the fact, disclosed by inquiries sent to the laboratory, that physicians were found willing to employ an arsenical preparation (Venarsen), advertised for intravenous use, although its promoters vouchsafed no information in regard to the nature of the arsenic compound contained therein.

UNRELIABILITY OF LITTLE USED DRUGS

The purpose of the federal Food and Drugs Act is to secure the prosecution and punishment of all who sell medicines which are adulterated or misrepresented as to composition. As a matter of fact, the wording of the law relating to the adulteration and misbranding of drugs is such that the federal authorities have been able to do little more than to require that the drugs for which standards are provided in the Pharmacopeia shall when sold comply with those standards. Similarly, those states which attempt to improve the quality of drugs sold within their borders — few states do efficient work along these lines — limit their work to the enforcement of the Pharmacopeial standards. This leaves the vast number of unofficial drugs and medicaments beyond the control of federal or state authorities. While most of these drugs are relatively unimportant, and while the amounts of them which are used are not great individually, the total consumption of them is large. With a view of furnishing to physicians standards for drugs of this sort the Council has described in New and Nonofficial Remedies not only distinctly proprietary drugs, but also some of the unofficial drugs which are apparently of therapeutic value and used to a considerable extent. Aiding the Council in this line of endeavor, the laboratory has attempted to establish standards for these little used drugs, and New and Nonofficial Remedies, 1916, provides standards for such unofficial and nonproprietary drugs as quinin and urea hydrochlorid, quinin tannate, sodium acid phosphate, and sodium

perborate. An example of work which furnished much needed standards for an unofficial article is the investigation of zinc permanganate by W. S. Hilpert.[3] Reference to the published reports of the laboratory will give an idea of the amount of work such standardization entails. A reference to the new U. S. Pharmacopeia, when this comes from the press, will show that a considerable number of unofficial articles described in New and Nonofficial Remedies have been admitted to the Pharmacopeia along with the standards worked out in this laboratory.

While in a way the work done in connection with these less important drugs has attracted little attention from the medical profession, it has had an effect on pharmaceutical manufacturers. In the past, pharmaceutical houses, ever anxious to market something new, on the slightest provocation have placed on the market, in the form of pills, powder, elixir, ampule, etc., every drug for which some sort of medical recommendation could be found. In marketing these dosage forms, the manufacturer has too often been little concerned about the quality of the drugs used.[4] Just at present, for instance, some interest is being shown in iron cacodylate; but while manufacturers appear to be most ready to take advantage of this interest by offering the drug in the form of ampules, etc., they have given little help toward the establishment of standards for this arsenic compound. Manufacturers are ever ready to sell drugs of all sorts, but in view of the small demand they cannot or will not safeguard the identity and purity of such drugs. A further illustration of the unreliability of unofficial drugs is the recent report by Levy and Rowntree[5] showing not only that the various dosage forms of emetin hydrochlorid obtained from different manufacturers varied from manufacturer to

3. Zinc Permanganate, THE JOURNAL A. M. A., Feb. 6, 1909, p. 488; Reports Chem. Lab., 1909, ii, 15.

4. The Unreliability of Unimportant Medicaments, THE JOURNAL A. M. A., Sept. 28, 1912, p. 1156.

5. Levy, R. L., and Rowntree, L. G.: On the Toxicity of Various Commercial Preparations of Emetin Hydrochlorid, Arch. Int. Med., March, 1916, p. 420.

manufacturer, but also that the product of the same manufacturer was variable and that the supply furnished by one pharmaceutical firm was so toxic as to make its use dangerous.

THE ANALYSIS OF "PATENT MEDICINES"

In the preface to the first annual report of the chemical laboratory it was stated that the laboratory "occasionally takes up the examination of 'patent medicines' . . ." At that time it was felt that the widespread use by the medical profession of irrational and even secret medicines made it necessary to devote the laboratory's attention to the correction of this evil. As the years have passed on, these conditions have been remedied to some extent, at least so far as chemical analysis can correct them. On the other hand, public opinion has been aroused to the many evils connected with the exploitation of "patent medicines," and has more and more insistently demanded that the medical profession aid in the correction of this evil. Accordingly, the laboratory has paid much attention to the analysis of "patent medicines" during the last few years. As the chief asset of "patent medicines" is the element of secrecy which surrounds their composition, it is hoped that the laboratory's analysis of such widely used "patent medicines" as Nature's Creation,[6] Mayr's Wonderful Stomach Remedy,[7] Sanatogen,[8] Eckman's Alterative,[9] Tonsiline,[10] and Bromo-Quinin[11] has been worth the labor. In addition, the work of this laboratory has been published, including not only the results of its analyses, but also the methods which are used. In view of the dearth of published reports regarding the methods used in the analysis of "patent medicines," it is hoped that this

6. THE JOURNAL A. M. A., March 5, 1910, p. 806.
7. THE JOURNAL A. M. A., Aug. 19, 1911, p. 671.
8. THE JOURNAL A. M. A., April 20, 1912, p. 1216.
9. THE JOURNAL A. M. A., April 27, 1912, p. 1298.
10. THE JOURNAL A. M. A., April 4, 1914, p. 1109.
11. THE JOURNAL A. M. A., Nov. 27, 1915, p. 1932.

feature of the laboratory's work has been of aid to chemists engaged in similar work.

The laboratory's actitives along these lines have done much to discount the claim of proprietary manufacturers that chemical analysis is unable to determine the character of "patent medicines." The recent Wine of Cardui trial has brought it out prominently that chemical analysis can determine the presence of potent constituents, and that "patent medicines" which fail to reveal such potent ingredients to the analyst may safely be put down as worthless. The demonstration that the essential composition of medicinal preparations may be determined by chemical analysis should also prove an effective answer to the manufacturers in their protest against the requirement, now being urged for enactment into law in various states, that the medicinal ingredients of their wares must be declared on the label. Manufacturers have held that this would lay them open to competition with imitations and substitutions. The possibility of chemical identification proves, however, that secrecy of composition, though it prevents consumers from knowing the character of a "patent medicine," will not be a hindrance to the imitator and substitutor.

IDENTITY OF DRUGS USED IN INVESTIGATIONS

In the past, much of the experimental work in medicine has seriously suffered in that the identity of the material used in such investigations was not established. In view of this the laboratory has watched the contributions submitted to THE JOURNAL, and whenever necessary and feasible has urged the authors to identify their material before publication of the findings. For instance, a number of staining agents — so-called "anilin dyes" — have been found to possess therapeutic action. Since the identity of many of these staining agents is today essentially secret, the laboratory has urged through THE JOURNAL that those who experiment with these substances make an effort to determine their identity whenever possible and to give

preference to those the chemical identity of which is known. The need for such identification has been discussed in the reports of the laboratory.[12] The amount of work involved in the chemical identification of drugs used for experimental work is illustrated in a contribution entitled "An Examination of Several Commercial Specimens of Opium Alkaloids or Their Salts,[13] by L. E. Warren, in which was determined the identity of the various opium products used in an investigation by D. I. Macht, carried out under a grant of the Therapeutic Research Committee.

THE LABORATORY AND PHARMACEUTICAL LITERATURE

In the past much of the information in regard to the composition and properties of medicines which has appeared in pharmaceutical journals has not become available to medicine. In many cases medical journals could not afford to publish such data because this would have been contrary to the interest of their advertisers, and hence the publications regarding the irrational character of Lactopeptine, of Bromidia, etc., which appeared in the pharmaceutical journals did not become a matter of common medical knowledge. Through the laboratory an attempt has been made to keep the medical profession informed in regard to pharmaceutical literature. The laboratory has a good working pharmaceutical and chemical library, and subscribes to the important American and foreign pharmaceutical and chemical publications. The discussion of new remedies, such as medinal and sodium veronal,[14] salvarsan, atoxyl and arsacetin,[15] and neosalvarsan[16] soon after their introduction, illustrates the work of the laboratory along these lines.

12. Reports A. M. A. Chemical Laboratory, 1912, v., 102.
13. Am. Jour. Pharm., 1915, **87**, 439.
14. The Journal A. M. A., Jan. 23, 1909, p. 311.
15. The Journal A. M. A., Dec. 31, 1910, pp. 2303 and 2314.
16. The Journal A. M. A., Oct. 5, 1912, p. 1295.

THE LABORATORY'S EFFORTS TOWARD RATIONAL PRESCRIBING

The laboratory naturally is in thorough sympathy with the present day efforts toward a more rational use of drugs, as exemplified in the Council's publication "Useful Drugs." Two recent contributions of the laboratory may be cited as a further support of the movement for limiting prescribing to the more widely used drugs. In line with the general tendency of manufacturers to put out all sorts of modifications and asserted improvements over official substances, there have been placed on the market a number of preparations said to represent some improvement over the pharmacopeial Blaud pills. The report, "The Quality of Commercial Blaud's Pills,"[17] by L. E. Warren, shows that the ordinary pharmacopeial Blaud pill is in every way the equal of the semiproprietary preparations claimed to be improvements. Further, the examination of the various brands of sodium and theobromin salicylate as compared with the preparation diuretin by P. N. Leech[18] shows that the former preparations, sold at 35 cents per ounce at the time the examination was made, are fully the equal of the proprietary Diuretin, which then cost the druggist $1.75 per ounce.

THE LABORATORY AS AN INFORMATION BUREAU

It is generally admitted that the proprietary medicine business, particularly the exploitation of complex mixtures, attained the extensive vogue which it has or had because instruction in medical schools was deficient in materia medica, pharmacy and chemistry. As a result of lack of knowledge along these lines, the young graduate after some trial became fearful of formulating his own prescriptions, and in time became dependent on pharmaceutical firms which provided him with medicines ready to dispense. That physicians

17. The Journal A. M. A., April 17, 1915, p. 1344.
18. The Journal A. M. A., April 4, 1914, p. 1108.

have been insufficiently trained in regard to the pharmacy and chemistry of drugs has often been emphasized in pharmaceutical journals where prescriptions containing incompatible drugs are reported and where even plans are brought forward whereby the pharmaceutical profession may aid in remedying this difficulty.

During my pharmaceutical experience I was often sorely vexed as to what to do when prescriptions contained drugs which on mixing would undergo decomposition which the physician surely did not anticipate. I remember well a prescription directing that potassium permanganate be made into pills with extract of gentian and other things, and how, the physician having spurned the suggestion to modify the prescription so as to avoid decomposition of the permanganate, I was obliged to select a mortar, gently triturate the drugs until a conflagration was started, and to finish the prescription after the combustion had subsided. However, in my pharmaceutical experience I generally found the physician most ready to receive suggestions from the pharmacist which would prevent incompatibilities, improve the palatability and appearance of his prescriptions, and protect the patient from unnecessary expense.

Similarly it has been my experience since the establishment of the Association's laboratory that physicians are anxious to receive information in regard to the materia medica, pharmacy and chemistry of drugs. As the druggist earns the respect and support of the physician when he makes available to him the pharmaceutical knowledge and experience which he has, so this laboratory has aimed to gain the endorsement of the American Medical Association membership by furnishing to physicians information in regard to the composition, chemistry and pharmacy of drugs through replies in the Query and Minor Notes Department of THE JOURNAL as well as through direct correspondence. It has been most gratifying to the laboratory that THE JOURNAL receives an increasing number of inquiries both as regards the chemical and pharma-

ceutical questions involved in the writing of prescriptions and as regards the composition of secret and semisecret proprietaries (often because they are prescribed by the inquirer's colleague) and "patent medicines" (which are taken by his patient). The laboratory has tried its best to answer the many inquiries received. Many of the questions which come in can be answered by a pharmacist or chemist without hesitation. Others, particularly as to the composition of medicines, the laboratory has been able to answer by reference to its library and its extensive card index. Still others have required experimentation and chemical analysis.

While, as stated a moment ago, the laboratory has encouraged the sending of inquiries and has earnestly striven to furnish the information asked for, it is obvious that the amount of chemical work which can be done is limited. The small size of the laboratory force, consisting of three chemists engaged in actual analytical work, makes it necessary to select for investigation those problems which shall be of general interest to the medical profession. As the American Medical Association is national in its scope, the laboratory has held that it can do analytical work only when such work will be of general interest to physicians and of value both to the medical profession and the public. In view of this it has refrained from undertaking analyses which would benefit only the physician making the inquiry and possibly his patient. The laboratory further has not felt justified in undertaking work of merely local interest; instead it has used its endeavors to secure the investigation of such local problems by municipal or state authorities.

PART II

REPORTS ABSTRACTED FROM THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

INCOMPATIBILITY OF ANTIMONY AND POTASSIUM TARTRATE AND SODIUM BICARBONATE

(Abstracted, with additions, from The Journal A. M. A., Aug. 5, 1916, p. 462)

The following inquiry was referred to the laboratory:

"The following prescription is published in a recent journal under the name of a 'yaws mixture' and is recommended for kala-azar:

℞	Antimon. et. Pot. Tartr.	gr.	1
	Sod. Salicyl.	gr.	5-10
	Pot. Iodid.	dr.	1
	Sod. Bicarb.	gr.	15
	Aq. ad.	oz.	5

"The foregoing is one dose to be given three times a day for adults. Sometimes the potassium iodid has to be reduced to 15 grains.

"The main object of the treatment is supposedly the administration of antimony, and I am wondering in what form the antimony occurs in this mixture, and if as a matter of fact it is soluble or, indeed, absorbable. The author states that the mixture is 'inelegant owing to the bicarbonate of soda, but this decreases the emetic properties of the mixture.' I find that a mixture of a 2 per cent. solution of tartar emetic with a 4 per cent. solution of sodium bicarbonate produces a white precipitate. Perhaps the reason the above-described mixture is not emetic is that the antimony is insoluble. I should be glad of any light that you can throw on the question.

"SAMUEL COCHRAN, M.D., Hope Hospital,
Hwaiyuan Anhwei, China."

It is well known that antimony and potassium tartrate is decomposed by alkalies. It was, therefore, to be expected that, though sodium bicarbonate might not decompose the antimony salt, decomposition would occur in time because of the increased alkalinity caused by the loss of carbon dioxid which escapes from aqueous solutions of sodium bicar-

bonate under ordinary conditions. This was confirmed by experiment and the following reply made to the inquiry:

"Tartar emetic and sodium bicarbonate mixed in aqueous solution in the proportions given in the prescription form no immediate precipitate; but on standing some time (for example, over night) a sediment appears on the bottom of the flask. This deposit or precipitate, when filtered off, washed with water and dissolved in hydrochloric acid, gives with hydrogen sulphid the characteristic orange-colored precipitate of antimony sulphid.

"In all probability, since there is no immediate precipitation, there is a slight loss of carbon dioxid and resultant increase in hydroxyl ion concentration, permitting hydrolysis of the complex tartrate ion and precipitation of antimony hydroxid.

"It is quite likely that the relative insolubility of the antimony compound which is precipitated out renders the absorption of antimony slower and in this way decreases its emetic properties."

DR. MILES' RESTORATIVE NERVINE

(Abstracted, with additions, from The Journal A. M. A., Sept. 9, 1916, p. 827)

Miles' Restorative Nervine is one of several "patent medicines" put out by the Miles Medical Company of Elkhart, Ind.

According to the trade package this "nervine"

"Is recommended for the Following Ailments: Epilepsy, Hysteria and St. Vitus's Dance. Nervousness, Sleeplessness, Neuralgia, Nervous Dyspepsia and Nervous Prostration. Headache, Backache, and Palpitation of the Heart due to functional or Nervous Disturbances. This remedy is also useful as an aid to other treatment for Tobacco and Alcoholic Excess, the Opium and Morphine Habits."

Three bottles of Miles' Restorative Nervine were used for the analysis. They contained a brown liquid having a sweet saline taste and an odor of a mixture of flavoring oils among which the odor of oils of lemon and cloves could be detected.

The specific gravity of the liquid at 15.6 C. was 1.3485.

Qualitative tests demonstrated the presence of ammonia (combined form), potassium, sodium, a small amount of calcium, a trace of iron, bromin, a small amount of chlorine, and sulphate ion, and benzoic acid (combined form), sugar, and color resembling caramel. No iodin, arsenic, heavy

metals, magnesium, alkaloids, acetanilid, acetphenetidin, salicylates, acetyl salicylic acid or alcohol was found present.

Quantitative determinations yielded the following results:

Ammonia (NH_3)	0.141	per cent.
Potassium (K^+)	2.40	per cent.
Sodium (Na^+)	1.32	per cent.
Calcium (Ca^{++})	.06	per cent.
Chlorid (Cl^-)	0.11	per cent.
Bromid (Br^-)	9.45	per cent.
Sulphate ion (SO_4^{--})	.054	per cent.
Benzoic acid	0.53	per cent.
Sucrose (cane sugar)	34.7	per cent.
Reducing sugars (calculated as invert sugar)	5.40	per cent.

From a consideration of the foregoing analysis it seems that this preparation could be duplicated in all its essentials by the following formula:

Ammonium bromid (NH_4Br)	1.13 gm.
Potassium Bromid (KBr)	9.87 gm.
Sodium bromid	6.93 gm.
Sodium chlorid	0.24 gm.
Sodium benzoate	0.85 gm.
Sugar	54.0 gm.
Caramel, sufficient to color	
Oil of lemon and cloves to flavor	
Water to make	100.00 c.c.

The average dose for an adult is given as two teaspoonfuls: Assuming one teaspoonful to be equivalent to 4 c.c., the total bromid content, corresponds to 23.4 grains potassium bromid. This dose is given three times a day and hence the daily dose contains bromids equivalent to 70 grains potassium bromid.

When publishing the results of this examination, THE JOURNAL concluded:

"From the chemists' report it appears that 'Dr. Miles' Restorative Nervine' is another one of the numerous bromid mixtures that have become so common since the passage of the Food and Drugs Act. The bromids, while powerful drugs, are not among those that the federal law requires must be declared, both qualitatively and quantitatively, on the label. The well marked physiologic effects of the bromids impress the public with the potency of any nostrum that contains them.

"Every carton of the 'Nervine' bears the statement in large letters:

"'Dr. Miles' Restorative Nervine contains no alcohol, opium, morphine, heroin, chloral hydrate, chloroform, cocain, alpha or beta eucaine, cannabis indica or acetanilid."

"It fails to mention that the nostrum does contain very definite quantities of the depressing bromids which, when taken in ignorance of their presence, may dose the sufferer into physical and mental inactivity. No wonder the 'patent medicine' interests fight formula disclosure."

Details of Analysis

The analysis was carried out according to the methods described in the Annual Report of the Chemical Laboratory (1915, viii, 52), except that instead of measuring out a portion of the sample, diluting to volume and using an aliquot, the sample for each analysis was weighed (after placing in a glass stopped weighing bottle).

Alcohol.—The specific gravity of the distillate at $\frac{25°}{25°}$ C. was 1.0001, showing the absence of alcohol.

Ammonia.—(*a*) The distillate from 15.317 gm. of the sample required for neutralization 12.66 c.c. tenth-normal acid, equivalent to 0.02159 gm. NH_3 or 0.1409 per cent.

(*b*) The distillate from 15.121 gm. required for neutralization 12.47 c.c. tenth-normal acid, equivalent to 0.02124 gm. NH_3 or 0.1405 per cent.

Sodium and Potassium.—(*a*) 5.060 gm. of the sample yielded 0.4778 gm. of the combined sulphates and 0.3045 gm. of platinum. From these data there should be 2.411 per cent. potassium (K^+) and 1.317 per cent. sodium (Na^+) in the sample.

(*b*) 3.345 gm. yielded 0.3150 gm. of combined sulphates and 0.2002 gm. platinum. Hence there should be 2.398 per cent. potassium (K^+) and 1.319 per cent. sodium (Na^+) in the sample.

Bromids and Chlorids.—Bromids and chlorids were determined by Method II of the Laboratory Report cited above.

(*a*) 8.051 gm. yielded on precipitation with silver nitrate 1.8419 gm. silver halids (bromid and chlorid) = 0.2288 gm. silver halid per gm. of sample.

(*b*) 3.4374 gm. yielded 0.7863 gm. silver halid = 0.2288 gm. silver halid per gm. sample.

(*c*) The precipitate of silver bromid and chlorid obtained from 2.8938 gm. of the sample, after solution in ammonia and precipitation by potassium iodid yielded 0.8344 gm. silver iodid or 0.2884 gm. silver iodid per gm. sample.

(*d*) The silver bromid and chlorid precipitate from 3.4712 gm. yielded 1.0014 gm. silver iodid or 0.2885 gm. silver iodid per gm. sample.

Using the value for silver bromid and chlorid per gm. obtained in *a* and that for silver iodid obtained in *c* in the calculation we obtain the values bromid (Br^-) 9.459 per cent. chlorid (Cl^-) 0.111 per cent.

Using the values obtained in *b* and *d* we obtain the values bromid (Br^-) 9.447 per cent. chlorid (Cl^-) 0.114 per cent.

Calcium.—(*a*) The calcium was precipitated from 20.553 gm. as oxalate in the usual manner and ignited to CaO. The residue weighed 0.0177 gm., equivalent to 0.062 per cent. Ca^{++}.

(*b*) The calcium oxid obtained from 19.721 gm. of the sample weighed 0.0185 gm., equivalent to 0.067 per cent. Ca^{++}.

Sulphate.—7.047 gm. of the sample, when treated with barium chlorid, yielded a precipitate of barium sulphate weighing 0.0092 gm., equivalent to 0.054 per cent. sulphate ion (SO_4^{--}).

Benzoic Acid.—A sample of from 20 to 30 gm. was acidified, subjected to steam distillation and the distillate received in a measured volume of standard alkali solution.

The distillation was continued until 150 c.c. or more of the distillate was collected.

The excess of standard alkali solution was then titrated with standard acid solution.

(*a*) The distillate from 18.42 gm. required 8.0 c.c. tenth-normal alkali for neutralization, equivalent to 0.097 gm. benzoic acid, or 0.52 per cent.

(*b*) The distillate from 35.00 gm. required 12.1 c.c. tenth-normal alkali for neutralization, equivalent to 0.148 gm. benzoic acid, or 0.43 per cent.

Benzoic Acid Identification.—These combined distillates after titration were nearly saturated with salt, acidified and shaken with ether. The ether was separated, washed with a little water and allowed to evaporate spontaneously.

On gentle heating the crystalline residue readily sublimes, the sublimed crystals having the typical form and the vapors having the peculiar odor of sublimed benzoic acid.

A solution of a portion of the crystals in hot water gives the usual flesh colored precipitate with ferric chlorid solution.

When a portion of the crystals were warmed with a few drops of alcohol, and a drop or two of concentrated sulphuric acid, the odor of ethyl benzoate was noted.

The melting point of the sublimed crystals was taken and found to be 119° C. uncorrected. (Melting point given for benzoic acid 121° corrected.)

Sugars.—13.680 gm. of the sample was placed in a 50 c.c. flask with about 25 c.c. of water. Lead acetate solution was then added till a precipitate no longer formed, and the solution then made up to the mark. The excess of lead was removed by dry sodium oxalate.

This solution was then polarized in a 1 decimeter tube at 20° C. and gave a rotation of + 6.80°.

Twenty-five c.c. of the solution was then inverted according to the method given in Bureau of Chemistry Bulletin 107.

The resulting solution was polarized in a 1 decimeter tube, and gave a rotation of + 0.90°.

Since the inverted solution had been diluted to twice the volume, we multiply this value by 2 = 1.80° angular.

$$6.80+1.80=8.60° \text{ angular}—24.80° \text{ Ventzke}$$

Sucrose present =

$$\frac{24.80}{142.66} — 20/2\times 26.=4.750 \text{ gm.}=34.7 \text{ per cent.}$$

Reducing Sugars.—Ten c.c. of the original solution above mentioned, representing 2.736 gm. of the sample, were used. 0.3142 gm. Cu_2O were obtained, equivalent to 0.1477 gm. invert sugar, giving 5.4 per cent. reducing sugar as invert.

Sucrose by Inversion and Reduction.—Three c.c. of the inverted sample, representing 0.4560 gm. of the original sample yielded 0.3962 gm. of cuprous oxid (Cu_2O), equivalent to 0.1917 gm. of invert sugar. From this quantity is substracted 0.0222 gm., for the reducing sugar present (calculated from the foregoing). Therefore the remaining 0.1695 gm. invert sugar from sucrose corresponds to 0.1610 gm. sucrose or 35.3 per cent.

Alkaloids.—After evaporating the chloroform extract obtained by the method described by Dr. Leech (loc. cit.) no noticeable residue remained, thus demonstrating the absence of any appreciable amount of alkaloidal material.

SULFURYL MONAL

(Abstracted, with additions, from The Journal A. M. A., Sept. 16, 1916, p. 894)

Sulfuryl Monal is said to be manufactured by Monal Frères, Nancy, France. It is sold in the United States by George J. Wallau, Inc., New York.

According to the label:

"Each Pastille { Contains: Sulfuryl (combined polysulphurets) = 0.35 centigr." Liberates: Nascent sulphuretted Hydrogen = 2 cub. cent."

The consideration of this preparation was taken up by the Council on Pharmacy and Chemistry and this laboratory was requested to check the claimed hydrogen sulphid content.

Details of Analysis

An original bottle of Sulfuryl Monal was used. It contained about twenty-five large, flat tablets having the taste of licorice extract and an odor of hydrogen sulphid. On addition of dilute acid the odor of hydrogen sulphid became pronounced.

The available hydrogen sulphid was determined by the evolution method involving the use of cadmium sulphid employed for the determination of sulphur in steel. Two pastilles were powdered in a mortar and placed in the generating flask of the evolution apparatus. Air was drawn through the apparatus for fifteen minutes and finally the water in the generating flask gently boiled for ten minutes. No trace of a precipitate of cadmium sulphid appeared, thus demonstrating that the tablets contained no appreciable amount of free hydrogen sulphid. The flask containing the specimen under examination was cooled and then 5 c.c. strong hydrochloric acid diluted with an equal volume of water added, and the operation of drawing the gases through the absorption liquid described above repeated. The cadmium sulphid produced was filtered off, washed and mixed with 300 c.c. water. Five c.c. strong hydrochloric acid was added, then 15 c.c. volumetric iodin solution (equivalent to 15.15 c.c. tenth-normal sodium thiosulphate solution) added and allowed to stand ten minutes.

A. Titration of excess of iodin required 5.62 c.c. tenth-normal sodium thiosulphate; hence 9.53 c.c. tenth-normal iodin solution (each cubic centimeter representing 0.0017 gm., or 1.2 c.c. H_2S) were consumed, indicating the presence of 0.0162 gm., or 11.4 c.c. H_2S (5.6 c.c. per tablet).

B. Titration of excess iodin required 4.10 c.c. tenth-normal thiosulphate solution, iodin equivalent to 11.05 c.c. having been consumed, indicating the presence of 0.0188 gm. or 13.2 c.c. H_2S (6.6 c.c. per tablet).

The claimed hydrogen sulphid content of Sulfuryl Monal was thus confirmed. Since there appeared to be no warrant for the claims that these pastilles possess exceptional therapeutic virtues, however, the Council held Sulfuryl Monal ineligible for New and Nonofficial Remedies (THE JOURNAL A. M. A., Sept. 16, 1916, p. 894).

NAPHTHALENE IN GASOLINE FOR AUTOMOBILES

(Reprinted, with additions, from The Journal A. M. A., Sept. 16, 1916, p. 897.)

A subscriber to THE JOURNAL sent in some Inajiffi Fuel Tablets (Inajiffi Fuel Company, Akron, Ohio) along with a circular advertising them. The circular read in part:

"More Power for Less Money
IMPORTANT
TO Automobile, Motorcycle,
Motorboat Owners,
Operators and Dealers
Inajiffi Prepared Gasoline is 100% Efficient.
Contains neither Alcohol, Acid, Ether or Camphor.
Serves You Quickly, Faithfully, Economically
You will Never Know the meaning of Real Engine Economy and Efficiency until you experience the quiet, smooth, easy-running and augmented power features produced by INAJIFFI."

The tablets had the odor of naphthalene and also the general physical properties of this substance; the material of the tablets melted at about 80 C. and this melting point was not changed materially when the tablet material was mixed with naphthalene; it was readily and completely soluble in chloroform and burned on ignition without leaving an appreciable residue. When the material was treated to form the picrate according to Mulliken (Identification of Organic Compounds, vol. 1, p. 201) a substance was obtained which melted at 150.5-151.5 C., uncorrected. This agreed closely with the melting point of naphthalene picrate, which is stated to melt at 150 C., uncorrected. The examination shows that the tablets consist to a large extent, if not entirely, of naphthalene.

In reply to an inquiry the following informal expression from a physical chemist, holding a research fellowship in the Mellon Institute, was received:

"I have had some experience with naphthalene dissolved in gasoline as a fuel for internal combustion engines, and can say that there is very little advantage to be gained by this procedure. Owing to its high carbon content, naphthalene does give added energy to the gasoline solution in which it is dissolved, but this solubility is so low that the gain is not important. Also, for perfect utilization of this added carbon, more air is required in the mixture, a fact not usually taken into consideration. The added energy contained in the few tablets that these dealers recommend to be added is assuredly quite too small to be noticeable.

"This opinion is as you requested, just an offhand answer to your question, but I believe it covers the ground completely."

Tablets of Naphthalene, recommended as an addition to gasoline, have also been marketed as "Cheep Gas" Tablets (*Jour. Am. Pharm. Assn.*, July, 1916, p. 716) and Tankii Tablets (*Druggists Cir.*, July, 1916, p. 416).

KORA-KONIA

(Reprinted, with additions, from The Journal A. M. A., Sept. 30, 1916, p. 1034)

Kora-Konia is a "dusting powder" which at present is advertised to the medical profession. It is put out by the Gerhard Mennen Chemical Company, Newark, N. J., which has become known to the public through the sale of various toilet preparations such as talcum powder, shaving soap, etc.

In view of the therapeutic claims which are made for this powder and because the advertising matter sent out vouchsafed no statement as to its quantitative composition, the Council on Pharmacy and Chemistry requested this laboratory to analyze Kora-Konia.

Kora-Konia was found to be a white powder, somewhat greasy to the touch. Qualitative tests showed the presence of boric acid, zinc, magnesium, a solid fatty acid and material insoluble in hydrochloric acid containing magnesium and aluminum. Starch was not found. Quantitative determinations gave the following results:

Acid-insoluble material (talc)	48.3 per cent.
Magnesium (Mg^{++}) soluble in dilute acid	1.2 per cent.
Zinc (Zn^{++})	4.5 per cent.
Stearic acid (impure)	39.2 per cent.
Boric acid	3.0 per cent.
Carbon dioxide (CO_2)	1.5 per cent.

From this analysis the composition of Kora-Konia was concluded to be essentially the following:

Zinc stearate U. S. P.	44 per cent.
Talc	48 per cent.
Magnesium carbonate U. S. P.	5.0 per cent.
Boric acid	3.0 per cent.

Essentially this dusting powder consists of the well-known substances talc and zinc stearate in about equal proportions, to which small quantities of magnesium carbonate and boric acid have been added.

Inasmuch as the claim is made, at least by implication, that Kora-Konia represents original investigation carried out "with the cooperation of the medical profession" it should be stated that the preparation of commercial zinc stearate was described and recommended as a dusting and toilet powder in 1892 (Proceedings Am. Ph. Assn., 1892, xl, 488).

The Council held that there is nothing new or original in any one of these substances or in the combination; that the extravagant and unwarranted claims made for this simple

dusting powder were undoubtedly leading the public, as well as some thoughtless physicians, to place undeserved confidence in it, and that in view of the small amount of boric acid present in the powder, its antiseptic powers must be slight and its germicidal powers almost nil.

Details of Analysis

One-half gm. of Kora-Konia was treated with about 25 c.c. of dilute hydrochloric acid (5 per cent.) and the mixture warmed on the steam bath for from half an hour to one hour. After cooling the liquid was filtered and the residue washed with warm water. The solution was reserved for the determination of zinc and magnesium.

The residue on the filter was allowed to dry in the air. When completely dry, it was treated with chloroform, which was allowed to run through the filter into a tared beaker. The treatment of the residue with chloroform was repeated until a few cubic centimeters of the chloroform filtrate on evaporation left no residue. The chloroform solutions were then evaporated on the steam bath, dried at 100 C. and weighed. This procedure yielded: (*a*) 0.1962 gm. stearic acid, which equals 39.24 per cent.; (*b*) 0.1952 gm., which equals 39.04 per cent. The melting point of the stearic acid thus obtained was found to be 56-57 C., uncorrected. The melting point usually given for stearic acid is 69 C. The commercial acid, however, usually has a much lower melting point, owing to slight admixture of palmitic acid, etc.

The U. S. P. IX requires that the melting point for stearic acid shall not be lower than 56 C.

After the removal of the stearic acid the filter was again allowed to dry. It was then inverted on a piece of glazed paper. The larger part of the residue separated from the filter paper and fell on the paper. The filter paper was then placed in a tared silica dish and ignited at a low heat. The remainder of the residue on the glazed paper was then added and the whole gently heated well above a low flame for a few minutes, then cooled in a desiccator and weighed. The residue weighed: (*a*) 0.2417 gm., which equals 48.34 per cent. talc; (*b*) 0.2409 gm., which equals 48.18 per cent.

The acid solution mentioned above was made barely alkaline with ammonia, and the zinc precipitated as sulphid. The zinc sulphid was filtered off, the filtrate and washings being saved for the determination of magnesium, then dissolved in hydrochloric acid, hydrogen sulphid boiled off, neutralized with ammounia and precipitated by ammonium phosphate as zinc ammonium phosphate. The precipitate was transferred

to a Gooch crucible, washed with dilute ammonium phosphate solution, then with 50 per cent. alcohol, and dried at 100 C. and weighed.

The precipitate of zinc ammonium phosphate weighed: (*a*) 0.0602 gm., which corresponds to 0.0222 gm. of zinc, or 4.44 per cent.; (*b*) 0.0612 gm., which corresponds to 0.0224 gm. of zinc, or 4.48 per cent.

The filtrate from the precipitations of zinc as sulphid was slightly acidified, the hydrogen sulphid boiled off and after cooling the magnesium was precipitated as magnesium ammonium phosphate. After filtration the precipitate was dried, ignited to the pyrophosphate cooled in a desiccator and weighed. The weight of the pyrophosphate obtained was: (*a*) 0.0283 gm., which corresponds to 0.0062 gm. of magnesium, or 1.24 per cent.; (*b*) 0.0274 gm., which corresponds to 0.0060 gm. of magnesium, or 1.21 per cent.

Carbon dioxid was determined in the Knorr apparatus according to the method described on page 170, Bureau of Chemistry Bulletin No. 107.

The increase in weight (CO_2) obtained from a sample weighing 0.5 gm. was: (*a*) 0.0075 gm., or 1.50 per cent., carbon dioxid; (*b*) 0.0070 gm., or 1.40 per cent. carbon dioxid.

Boric acid was determined in the following manner: A 2 gm. sample was treated with a mixture of 5-7 c.c. strong hydrochloric acid and 25 c.c. water, and boiled for from fifteen minutes to half an hour under a reflux condenser. After cooling and filtering from the separated stearic acid and the insoluble talc, saturated solution of sodium carbonate was added in slight excess of the amount necessary to precipitate all the zinc and magnesium. This precipitate was then filtered out and the filtrate barely acidified to methyl orange. The solution was then boiled a few minutes to expel carbon dioxid. After cooling the solution was made exactly neutral to methyl orange with tenth-normal sodium hydroxid solution. Glycerin was then added and the solution titrated with tenth-normal sodium hydroxid, phenolphthalein being used as indicator. There were required for this titration: (*a*) 9.3 c.c. tenth-normal sodium hydroxid corresponding to 0.0577 gm. boric acid, or 2.89 per cent.; (*b*) 10.0 c.c. tenth-normal sodium hydroxid corresponding to 0.0620 gm. of boric acid, or 3.10 per cent.

In such a mixture the moisture cannot be determined satisfactorily since available methods would remove more or less water from the boric acid present.

HYDRAS

(Abstracted, with additions, from The Journal A. M. A., Oct. 7, 1916, p. 1107)

Hydras, sold by John Wyeth and Brother, Philadelphia, is one of the many proprietary "uterine tonics." It is stated to contain "cramp bark, helonias root, hydrastis, scutellaria, dogwood and aromatics," but the amounts of the several ingredients are not given.

The name "Hydras," taken in connection with the statement of composition, suggests that hydrastis (golden seal) is an important constitutent. In view of the nonquantitative and therefore meaningless statement of composition the chemical laboratory determined the amount of ether-soluble alkaloid contained in Hydras. As a result of this examination, the following report was made to the Council on Pharmacy and Chemistry:

The "hydrastine" content of Hydras was determined by extraction with immiscible solvents (*Pharmaceutical Review*, May, 1908, p. 132). It was found that 25 c.c. yielded an alkaloidal residue of 0.0160 gm. ether-soluble alkaloid (hydrastine). The preparation therefore contains not more than 0.64 gm. "hydrastine" per 100 c.c. Inasmuch as hydrastis is required to contain not less than 2.5 per cent. of ether-soluble alkaloid, Hydras contains the equivalent of not more than 2.66 gm. hydrastis in 100 c.c. and the stated dose, 1 dessertspoonful, or 8 c.c., represents not more than 0.2 gm. or one tenth of the U. S. P. average dose of hydrastis.

In view of the claims made for Hydras and the findings of the laboratory the council held that: The preparation is semi-secret; the recommendations for its use in specified diseases (which appear on the label and in the advertising accompanying the bottle) are certain to lead to its ill-advised use by the public; the claims made for its curative properties are exaggerated and unwarranted; in view of the small content of hydrastis, the name is misleading; finally, the combination of five drugs, even if individually they were of therapeutic value, is irrational.

NUXATED IRON

(Abstracted, with additions, from The Journal A. M. A., Oct. 21, 1916, p. 1244)

Nuxated Iron is a "patent medicine" sold by the Dae Health Laboratories, Detroit, Mich. It is extensively advertised in newspapers, and also in at least one medical publication, the *Medical Brief*.

According to the label, the tablets are to be taken:

". . . for general weakness, nervousness, anemia, lack of blood, malnutrition, lack of flesh caused by mal-assimilation, atonic dyspepsia and as a general tonic in 'rundown' or debilitated conditions of the system."

The wrapper of Nuxated Iron contains the following in regard to composition:

"Formula: The valuable blood, nerve force and tissue building properties of this preparation are due to organic iron in the form of ferrum peptonate in combination with nux vomica, phosphoglycerate de chaux and other valuable ingredients."

In the *Medical Brief* the following statement of composition—equally nonquantitative—is given:

"Iron Peptonate	Cascarin
Calcium Glycerophosphate	Magnesium Carbonate
Extract of Nux Vomica	Powdered Ginger."*

* We are informed that the company now, or after this analysis was made, claims that the formula of Nuxated Iron is:

Iron Peptonate	3/4 gr.
Calcium Glycerophosphate	3/4 gr.
Calcium Hypophosphate [Hypophosphite]	3/4 gr.
Ext. Nux Vomica	1/24 gr.
Cascarin	1/6 gr.
Mag. Carbonate	2 gr.
Po. Ginger	1/4 gr.
Oil Cassia Cinnamon q. s.	
In each tablet	

An original package of Nuxated Iron was found to consist of uncoated tablets each of which had an average weight of 0.324 gm.

Qualitative tests indicated the presence of iron, calcium, magnesium, a small amount of potassium, carbonate, glycerophosphate, small amounts of chlorid and a very small amount of strychnin. The presence of a small amount of cascara was indicated, but the presence of ginger could not be ascertained by means of the usual tests. The tablets contained a considerable quantity of vegetable fiber and smelled strongly of cinnamon, though this drug is not indicated by either "formula" given above.

Quantitative determinations yielded the following results:

Inorganic, acid insoluble material (talc?)	3.9	per cent.
Mg^{++}	7.2	per cent.
Ca^{++}	7.5	per cent.
PO_4^{---}	5.1	per cent.
CO_3^{--}	14.8	per cent.
Fe^{+++}	3.1	per cent.
K^{+}	0.8	per cent.
Total alkaloids	0.04	per cent.

From a consideration of the foregoing it may be concluded that the tablets contained:

Magnesium carbonate, U. S. P.....29.8 per cent.
Calcium glycerophosphate (calculated from PO_4 found)...12.4 per cent.
Iron peptonate (calculated from iron found).....12.0 per cent.
Nux vomica, or its equivalent, not more than..... 3.2 per cent.

An independent laboratory was subsequently requested to purchase a specimen of Nuxated Iron and to determine the alkaloid and iron content thereof. It reported that the average weight of the tablets was 0.2915 gm., that the total alkaloid, determined according to the U. S. P. IX method of assay for extract of nux vomica, was 0.055 per cent. (which responded to tests for strychnin), and that the tablets contained 0.89 per cent. of iron (Fe).

In consideration of this report further specimens of Nuxated Iron were purchased by the laboratory of the American Medical Association and were examined.

The labels of the newly purchased specimens were identical in wording with those purchased previously, but the ornamentation and color of ink were different and indicated that the present specimens were from a different "lot" than those examined before.

One bottle was found to contain 60 tablets. The weight of the 60 tablets was 17.686 gm., or an average of 0.2948 gm.

The iron content was determined by the method used in the first analysis. The tablets were found to contain iron compounds equivalent to 1.01 and 0.93 per cent. of iron (Fe), or an average of 0.97 per cent. By using the volumetric method followed by the independent laboratory the iron found was equivalent to 0.79 and 0.85 per cent.; average 0.82 per cent.

In discussing the asserted non-secrecy of Nuxated Iron and the unsatisfactory nature of the statements of composition THE JOURNAL stated that it:

". . . felt that it owed it to the public to find out just how much iron and nux vomica there were in 'Nuxated Iron.' Packages of the nostrum purchased on the open market were subjected to analysis both in the Chemical Laboratory of the American Medical Association and elsewhere. Qualitative tests indicated the presence of iron, calcium, magnesium, carbonate, glycerophosphate and small amounts of potassium and chlorid and the presence of cascara. Quantitative examinations were made and, so far as the essential ingredients—

nux vomica and iron—of the nostrum are concerned, gave the following results:

Total nux vomica alkaloids, per tablet.....1/500 grain
Iron (Fe) per tablet.....1/25 grain

"According to these analyses there is only one-twenty-fifth of a grain of iron in each 'Nuxated Iron' tablet, while the amount of nux vomica, as expressed in terms of its potent alkaloids, is practically negligible. If a person wants to take iron on his own responsibility—and this cannot be recommended—it is possible to get this drug in a stable form in the well-known Blaud's Pills. In a dollar bottle of 'Nuxated Iron' the purchaser gets, according to our analysis, less than 2½ grains of iron; in 100 Blaud's Pills, which can be purchased at any drug store for from 50 to 75 cents, there are 48 grains of iron. . . .

"'Nuxated Iron' is essentially secret in composition and, while the public is led to believe that the preparation consists chiefly of nux vomica and iron, analyses indicate that it contains much less than an ordinary dose of iron and a negligible amount of nux vomica. It is sold under claims that are both directly and inferentially false and misleading, not only in regard to its composition, but also as to its alleged therapeutic effects."

Details of Analysis

Iron.—A sample was treated with water and a few cubic centimeters of strong sulphuric acid and the mixture evaporated until copious fumes appeared. It was then further heated until the excess of acid was driven off. The charred residue was leached out with dilute hydrochloric acid, the filtered solution made alkaline with ammonia water, the precipitate formed collected on a filter, washed with water and redissolved in hydrochloric acid. The iron was separated from this solution by the basic acetate process, supplemented by washing the final precipitate with sodium hydroxid solution to remove aluminum if present. (A) Five pills, weighing 1.6095 gm., gave 0.0702 gm. of ferric oxid, equivalent to 0.0490 gm. of iron, or 3.05 per cent. (B) Six pills, weighing 1.972 gm., gave 0.0890 gm. of ferric oxid, equivalent to 0.0622 gm. of iron, or 3.15 per cent.

Calcium.—The sample was boiled repeatedly with concentrated nitric acid, the solution evaporated to dryness, the residue taken up in a little hydrochloric acid and the phosphoric acid removed by the ferric chlorid method. After removal of the ferric phosphate and excess of iron salt as basic acetate, the calcium was precipitated in the usual way

as oxalate, ignited and weighed as oxid. (A) Two gm. of the material yielded 0.2091 gm. of calcium oxid, equivalent to 0.1495 gm. of calcium or 7.48 per cent. (B) Two gm. of the material yielded 0.2096 gm. of calcium oxid, equivalent to 0.1498 gm. of calcium, or 7.49 per cent.

Magnesium.—Magnesium ammonium phosphate was precipitated from the filtrates from the calcium determination, and weighed as magnesium pyrophosphate. (A) Two gm. of the material yielded 0.6589 gm. of magnesium pyrophosphate, equivalent to 0.1439 gm. of magnesium, or 7.20 per cent. (B) Two gm. of the material yielded 0.6601 gm. of magnesium pyrophosphate, equivalent to 0.1442 gm. of magnesium, or 7.21 per cent.

Phosphoric Acid.—A sample was boiled with nitric acid as described above, and the phosphoric acid precipitated from the resultant filtered solution as ammonium phosphomolybdate. The latter was dissolved in ammonia water, the phosphoric acid precipitated as magnesium ammonium phosphate, the precipitate collected, heated, and weighed as magnesium pyrophosphate. (A) Two gm. of the material yielded 0.1207 gm. of magnesium pyrophosphate equivalent to 0.1031 gm. of PO_4 ion, or 5.15 per cent. (B) Two gm. of the material yielded 0.1180 gm. of magnesium pyrophosphate, equivalent to 0.1008 gm. of PO_4 ion, or 5.04 per cent.

Potassium.—A sample was treated with concentrated sulphuric acid, the excess of acid driven off by heat, and the residue ignited. The residue was then leached out with water and the calcium salts removed by ammonium oxalate. After ignition and removal of ammonium salts, the magnesium salts were removed by barium hydroxid. The excess of barium salt was removed by sulphuric acid, and the final filtrate evaporated to dryness ignited and weighed. (A) One gm. of the material yielded 0.0161 gm. of potassium sulphate, equivalent to 0.0072 gm. of potassium, or 0.72 per cent. (B) Two gm. of the material yielded 0.0381 gm. of potassium sulphate, equivalent to 0.0172 gm. of potassium, or 0.86 per cent.

Inorganic Material Insoluble in Nitric Acid.—From 0.575 gm. of the material an insoluble residue weighing 0.0225 gm. was obtained, equivalent to 3.9 per cent.

Carbon Dioxid.—This was determined by the method described in Bulletin 107, Bureau of Chemistry, pp. 169 and

170. One gm. yielded 0.1084 gm. of carbon dioxid, equivalent to 0.1476 gm. of CO_3 ion, or 14.8 per cent.

Alkaloids.—The Stas-Otto process, as described in Autenrieth (Warren Translation) (1915 edition) pp. 57-59, was used. Sixteen pills, weighing 4.85 gm., yielded a combined alkaloidal residue which, on titration, required 0.3 c.c. of fiftieth-normal acid for neutralization. This is equivalent to 2.0 mg. of alkaloid, calculated as strychnin. The residue of alkaloid gave a satisfactory qualitative test for strychnin. The presence of brucin could not be determined on this small amount of material.

SECOND EXAMINATION

Iron (Gravimetric).—Using the method described above two samples of 2 gm. each, gave respectively, 0.287 gm. of ferric oxid, equivalent to 0.0202 gm. of iron, or 1.01 per cent., and 0.0264 gm. of ferric oxid, equivalent to 0.0185 gm. of iron, or 0.93 per cent.

Iron (Volumetric).—The material was decomposed and extracted according to the method described in the Laboratory Reports of the A. M. A., 1915, viii, 10. To the acid solution sulphuric acid was added and the mixture evaporated to expel hydrochloric acid and nitric acid. The solution was diluted, the iron reduced with a zinc-platinum couple and the reduced solution titrated with tenth-normal potassium permanganate solution. Two sample of 2 gm. each, yielded the following results: (*a*) required 2.8 c.c. of the potassium permanganate solution; (*b*) required 3.0 c.c. of the potassium permanganate solution. The potassium permanganate solution was equivalent to 0.00565 gm. of iron per cubic centimeter. Hence (*a*) contains 0.0158 gm. of iron, or 0.79 per cent.; (*b*) contains 0.0170 gm. of iron or 0.85 per cent.

O-DO-CURE

(Abstracted, with additions, from The Journal A. M. A., Dec. 30, 1916, p. 2030)

The following query from a correspondent was referred to the laboratory: What is the composition of "O-Do-Cure"? It is a perspiration remedy manufactured by the O-Do-Cure Toilet Company, Chicago.

The Laboratory answered: Two original bottles (price 50

cents each) of "O-Do-Cure" were examined. The following statements appeared on the label:

"A Daily Toilet Requisite for Perspiration.
A Perfect Deodorant Toilet Water.
Use it daily after the morning bath. It refreshes and purifies the pores; prevents odor—yet does not interfere with natural perspiration. Used freely to relieve tired, burning perspiring feet, it has no equal."

Each bottle of "O-Do-Cure" contained about 90 c.c. (3 fluidounces) of a green colored liquid, highly perfumed and having an acid reaction. The specific gravity at 15.6 was 0.9648. Qualitative tests demonstrated the presence of alcohol, boric and salicylic acids. The presence of 40 per cent. of alcohol was declared on the label. Quantitatively, each 100 c.c. was found to contain:

Alcohol (absolute)	34.00 Cc.
Boric acid (H_3BO_3)	5.95 gm.
Salicylic acid ($C_6H_4(OH)COOH$)	0.26 gm.

From the analysis, it is concluded that an essentially similar solution could be compounded as follows:

Salicylic acid	1 grain
Boric acid	30 grains
Alcohol	3 fluidrams
Perfume, sufficient	
Water to make	1 fluidounce.

Details of Analysis

Alcohol.—This was determined according to the procedure of "Official and Provisional Methods of Analysis," U. S. Department of Agriculture, Bulletin 107, p. 83. Twenty-five c.c. of the original (diluted to 130 c.c.) yielded a 100 c.c. of distillate having a specific gravity of 0.98841. This is equivalent to 34.0 per cent. alcohol by volume.

Salicylic Acid.—Ten c.c. of the original was diluted to 20 c.c. (with water) and shaken in a separator with four separate portions of chloroform. The chloroform extract was allowed to evaporate in a shallow beaker, and dried in a desiccator. A. The residue weighed 0.0262 gm. B. The residue weighed 0.0256 gm. Average salicylic acid = 0.26 gm. per 100 c.c.

Boric Acid.—Ten c.c. of the original was diluted with water to 50 c.c. and the solution made neutral with sodium hydroxid, using methyl orange as an indicator; 40 c.c. of glycerin was then added, and the mixture titrated with normal sodium hydroxid, using phenolphthalein as indicator. A. It required 9.56 c.c. of normal sodium hydroxid, equivalent to 5.92 gm.

of boric acid per 100 c.c. of original material. B. It required 9.64 c.c. of normal sodium hydroxid, equivalent to 9.58 gm. of boric acid per 100 c.c. Average, 9.61 gm. of boric acid per 100 c.c. of original material.

SALOFORM

(Abstracted, with additions, from the Annual Reports of the Council on Pharmacy and Chemistry, A. M. A., 1916, p. 71)

A referee submitted the following report of the American Medical Association Chemical Laboratory to the Council:

ANALYSIS OF SALOFORM

Saloform (Flexner) is advertised by the Robinson-Pettet Company of Louisville, Ky. In the advertisements for the product it is stated that:

"SALOFORM is a definite chemical compound the component parts of which are *Hexamethylene Tetramine, Salicylic Acid* and Lithia."

"As a Uric Acid Solvent it is indicated in *Rheumatism, Gout,* in *Phosphaturia,* in *Gravel,* and in *Renal Colic.*"

"As a Genito-Urinary Antiseptic it limits suppuration anywhere along the Urinary Tract, from the Kidneys down to the orifice of Urethra."

As, even after diligent search, no description of a compound of hexamethylenamine (hexamethylenetetramine), salicylic acid and lithia was found in chemical literature, it seemed probable that Saloform is merely a mixture of hexamethylenamine and lithium salicylate. Accordingly the separation of Saloform into its component parts by means of selected solvents was attempted. By triturating the powder with chloroform, filtering and evaporating the filtrate, a residue was obtained which gave satisfactory tests for hexamethylenamine but contained only traces of salicylic acid or lithium salicylate. The portion insoluble in chloroform was dissolved in water. The solution gave satisfactory tests for lithium salicylate but not for hexamethylenamine. From these tests it is evident that Saloform is a simple mixture of hexamethylenamine and lithium salicylate. Quantitative examination indicated that the two ingredients, hexamethylenamine and lithium salicylate, are present in approximately equal amounts.

Details of Analysis

Hexamethylenamine.—Total Nitrogen was determined by the Gunning method (*Bur. Chem. Bull.,* 107, p. 7) and the

normal acid neutralized by the ammonia calculated directly to hexamethylenamine.

$$1 \text{ c.c. of N-1 } H_2SO_4 = 0.034795 \text{ gm. of } C_6H_{12}N_4.$$

A specimen weighing 2.7516 gm. was dissolved in water, the solution diluted to 100 c.c. with water and aliquot portions of the solution taken for the nitrogen determinations. The nitrogen from 2.5 c.c. of the solution (representing 0.06879 gm. of original material) required 9.589 c.c. of normal sulphuric acid, equivalent to 0.333649 gm. of hexamethylenamine, or 48.5 per cent. A duplicate required 9.579 c.c. of normal sulphuric acid, equivalent to 0.333301 gm. of hexamethylenamine, or 48.45 per cent. Average, 48.48 per cent. of hexamethylenamine.

Lithium Salicylate.—Lithium salicylate was approximately determined by three methods. The first was by ignition of a weighed portion of the material with sulphuric acid and weighing as anhydrous lithium sulphate.

$$Li_2SO_4 \times 2.61623 = LiC_7H_5O_3.$$

From 0.5054 gm. of material, 0.0961 gm. of lithium sulphate was obtained, equivalent to 0.251417 gm. of lithium salicylate, or 49.74 per cent.; another determination was carried out in which the salicylic acid was removed by acidifying the aqueous solution of the material, filtering, shaking the filtrate with ether, evaporating the aqueous solution and igniting the residue with sulphuric acid. From 0.55032 gm. of the material, 0.1050 gm. of lithium sulphate was obtained, equivalent to 0.274704 gm. of lithium salicylate or 49.91 per cent.

The second method used for the determination of lithium salicylate was perfected by St. John for salicylic acid (*Jour. Assn. Off. Ag. Chem.*, 1915, **1,** 343). It was carried out for this analysis as follows:

A weighed quantity of the material was dissolved in water, about 0.2 gm. of sodium carbonate added, followed by sufficient iodin solution to color the liquid slightly yellow and the mixture warmed on the water bath, more iodin being added as the color became lighter. The rose-colored precipitate was washed twice by decantation with boiling water, collected on a weighed filter, washed with hot water, dried at 100 C. and weighed.

$$C_6H_2I_2O \times 0.4015 = C_6H_4.OH.COOH$$

From 0.4439 gm. of material 0.5375 gm. of the diiodo-compound was obtained, equivalent to 0.221181 gm. of lithium salicylate, or 49.82 per cent. From 0.4065 gm. of material

0.5104 gm. of the diiodo-compound was obtained, equivalent to 0.20495 gm. of lithium salicylate, or 50.41 per cent. Average, 50.11 per cent. of lithium salicylate.

The third method consisted in determining the salicylic acid directely and calculating to lithium salicylate. Salicylic acid was approximately determined as follows:

A weighed quantity of the material was dissolved in a few c.c. of cold water, the solution acidified with sulphuric acid, the mixture allowed to stand over night, the precipitate collected in a weighed Gooch crucible, washed with a few c.c. of cold water, dried at 60 C. and weighed. The filtrate and washings were united, the solution shaken with ether, the solvent washed with water, allowed to evaporate spontaneously, the residue dried at 60 C. and weighed.

From 1.4679 gm. of material, 0.5478 gm. of precipitate and 0.1308 gm. of ether extract was obtained; total, 0.6786 gm. of salicylic acid or 46.23 per cent. This is equivalent to 48.34 per cent. of lithium salicylate.

PART III

REPORTS NOT PREVIOUSLY PUBLISHED

WINE OF CARDUI

INTRODUCTION

Wine of Cardui is a preparation which is advertised and sold as a remedy for ailments peculiar to women. It is made and sold by the Chattanooga Medicine Company of Chattanooga, Tenn. A specimen of the preparation was examined in the Association's laboratory, and an abstract of the report of the analysis was published in THE JOURNAL (April 11, 1914, p. 1186). This appeared as part of an article in which the remedial claims made for the preparation by its manufacturers were criticized as being extravagant and untruthful and in which the methods of the manufacturers of the preparation were otherwise criticized. Later THE JOURNAL published an explanation of the article (June 6, 1914, p. 1827). Still later THE JOURNAL published another article concerning Wine of Cardui (July 18, 1914, p. 258), and in this the abstract of the analytic report was republished, the analysis in the interval having been verified by further analyses.

Suits against the American Medical Association and the editor of its journal were then filed on behalf of the Chattanooga Medicine Company and its owners. For verification of the published analytic reports another analysis of Wine of Cardui was made by the chemist who had made the first analysis. Additional analyses were made by two other chemists in the Association's laboratory.

In addition to the analyses of Wine of Cardui which were made in the Association's laboratory, it seemed

desirable that the preparation should be examined by other chemists. Accordingly several chemists who had no connection with the laboratory of the American Medical Association were requested to make an analysis of the product, and in most instances an analysis of synthetic preparations made from the supposed ingredients of Wine of Cardui. In addition to this two other chemists were asked to investigate certain phases of the problem.

Brief abstracts of the chemists' reports follow.

Four analyses of Wine of Cardui were made by Mr. Warren. His report[1] shows that the preparation is a brownish-red liquid, having a valerian-like odor, a bitter taste and a practically neutral reaction to litmus. About 20 per cent. of alcohol by volume was found. The solids amounted to about 3 gm. per hundred c.c. (13 grains per fluidounce). They consisted chiefly of vegetable extractives with a little caramel. Compounds of arsenic, antimony and mercury, iodids, bromids, benzoates, salicylates, tartrates, succinates, phenolphthalein, potent alkaloids, such as morphin and strychnin, emodin-bearing drugs, such as aloes, cascara and rhubarb, and emetic drugs, such as ipecac, lobelia and tobacco, were absent. A trace of iron was found, but the amount was too minute to merit any consideration from the therapeutic point of view. Small amounts of a nitrate were present. The ash amounted to about 0.75 gm. per hundred c.c. The small quantity of ash excluded the presence of saline purgatives, such as Epsom salt, magnesium citrate, etc., at least in therapeutically effective quantities. The absence of wine was demonstrated. Physiologic tests did not indicate the presence of any active drug in Wine of Cardui except alcohol. The presence of black haw was suspected, but from the resin determinations it was concluded that a dose of Wine of Cardui does not contain more than about one-eightieth as much resin as does one dose of fluidextract of black haw. From

1. This report is given on page 46.

the results of the several analyses, and from physiologic tests, Mr. Warren concluded that there is no potent drug in Wine of Cardui except the alcohol (at least in therapeutically effective amounts), and that the preparation should not be called a "wine."

The essential features of the work of Leech[2] are:

1. Wine of Cardui contains no potent ingredients, other than 20 per cent. of alcohol, as demonstrated by chemical and physiologic tests. The amount of iron was so minute as to be of no value.

2. The amount of volatile matter (other than steam and alcohol) was found to be 0.004 per cent. — too small for therapeutic effect.

3. Based on the valerate determinations, it would require about seventeen doses of Wine of Cardui to get the same valerate content as in one dose of fluidextract of *Viburnum prunifolium.*

4. The percentage of alcohol is too low to extract much of the drugs used. Hence excessive amounts of alcohol would be taken (in the form of Wine of Cardui) to obtain the same amount of viburnum as in the fluidextract.

5. Wine of Cardui is identical with a preparation made by percolating about 13 per cent. (gm. per c.c.) of *Carduus benedictus,* unchopped, and 1.4 per cent. of *Viburnum prunifolium,* bark of the stem (ground) with 20 per cent. alcohol. To the percolate is added 0.2 per cent. of caramel and 0.24 per cent. of anhydrous sodium carbonate; the percolate is then filtered.

Dr. Hilpert[3] analyzed a specimen of Wine of Cardui which was a mixture of the contents of a number of bottles of the preparation. His examination determined the absence of all of the substances (except alcohol) which are commonly recognized as possessing therapeutic merit or which are capable of producing

2. For the report of Dr. Leech see p. 57.
3. The report may be found on p. 72.

physiologic effects. His conclusion that Wine of Cardui is inert except for its alcohol was verified by swallowing five doses of the preparation and comparing its effects with those obtained from taking the same volume of 20 per cent. alcohol.

An analysis of Wine of Cardui was made by Prof. Albert H. Clark,[4] of the University of Illinois School of Pharmacy, from a specimen composed of a mixture of nine bottles of the product. Synthetic preparations were made from blessed thistle and black haw and the products analyzed by him. The results were compared with those obtained from genuine Wine of Cardui. Physiologic tests with Wine of Cardui were also conducted. Professor Clark's report shows that his analysis confirms in all essential particulars the findings obtained in the analyses by Mr. Warren, Dr. Leech and Dr. Hilpert. From the results of his analysis and physiologic tests, Professor Clark concludes that the preparation contains none of those drugs (except alcohol) which are considered active or potent. He believes that Wine of Cardui has essentially the same composition as the synthetic preparation.

Mr McAbee,[5] of the Indiana State Board of Health, analyzed six specimens of Wine of Cardui of ages varying from recent to several years. The color and general appearance of the several specimens were alike. Four possesed a valerian-like odor; *two* (thought to be the oldest) *did not*. The specimens varied in size from 275 to 300 c.c. (from 9 to 10 fluidounces); the specific gravity from 0.9865 to 0.9976; alcohol from 14.77 to 21.90 per cent. by volume; ash from 0.719 to 1.066 gm. per hundred c.c.; solids, from 2.605 to 3.825 gm. per hundred c.c., and ether extract from 0.0202 to 0.038 gm. per hundred c.c. No physiologically active substance was found. Mr. McAbee concludes that Wine of Cardui is a hydro-alcoholic solu-

4. For Prof. Clark's report see p. 78.
5. Mr. McAbee's report begins on p. 81.

tion of some drug containing a bitter principle, but that it contains no potent ingredient in quantities capable of producing any physiologic effects.

Prof. A. B. Stevens,[6] of the University of Michigan School of Pharmacy, made a critical examination of Wine of Cardui, and made synthetic preparations from its supposed ingredients, which he analyzed. From the results of his analysis of the market preparation and his physiologic tests with it, Professor Stevens concluded that:

Wine of Cardui does not contain any potent ingredient except alcohol; the preparation is not a wine, and the presence of 20 per cent. of alcohol in Wine of Cardui, without medicinally active constituents, permits its use as an alcoholic beverage.

From the analysis of the synthetic preparation he was convinced that Wine of Cardui is a hydro-alcoholic extract from small amounts of blessed thistle and black haw, the mixture being colored with caramel. Professor Stevens removed the alcohol from Wine of Cardui, and prepared the residual extractives for administration in capsules, pills and tablets. The extractives from the synthetic preparation were likewise so prepared. The dealcoholized Wine of Cardui was preserved in 40 per cent. glycerin, and was found to keep well. From these experiments Professor Stevens concluded that alcohol is not at all necessary in preserving the vegetable extractives in Wine of Cardui.

Dr. R. W. Webster,[7] of Rush Medical College, made an analysis of Wine of Cardui. He found 20.33 per cent. of alcohol by volume, about 3.5 gm. of solids per hundred c.c. (16 grains per fluidounce) and about 0.76 gm. of ash per hundred c.c. No potent substances except alcohol were found. Dr. Webster's findings, therefore, confirm in every essential particular those

6. For Dr. Stevens' report see p. 82.
7. The report of Dr. Webster may be found on p. 85.

obtained by the chemists whose reports are abstracted above.

Dr. Loevenhart[8] studied Wine of Cardui both from the chemical and the pharmacologic aspects. His pharmacologic conclusions will be discussed elsewhere. The quantitative chemical analysis of Wine of Cardui showed the presence of 20 per cent. of alcohol and about 3 per cent. of total solids. Small amounts of glucose, potassium nitrate and suspended matter were also recorded by him. As the chemical analysis revealed no potent constituents, other than alcohol, physiologic tests were made which yielded the same results. From a study of synthetic preparations, together with the general chemical analysis, Dr. Loevenhart's report shows that Wine of Cardui is an alcoholic solution (20 per cent. alcohol) containing small amounts of extractives from *Carduus benedictus* and *Viburnum prunifolium*. Even if these drugs have therapeutic value, the menstruum that is used in the preparation of Wine of Cardui is not a proper one to extract their virtues.

The special feature of the work of Dr. Emerson R. Miller[9] on Wine of Cardui was the estimation of the volatile matter. By careful determination (distillation with steam) he found the small amount of 0.002 per cent. of volatile matter (other than alcohol and water). This essentially confirms the work of Leech. Furthermore, as a correlating proof of the small amount of volatile matter, tests by means of the refractive indexes of the distillates from Wine of Cardui and from 23 per cent. alcohol demonstrated the correctness of Dr. Miller's first determination. Besides the alcohol, Dr. Miller found no active ingredients in Wine of Cardui, at least not in appreciable amounts.

8. Dr. Loevenhart's reports may be found on pp. 77 and 86.
9. Dr. Miller's report may be found on p. 47.

The above abstracts embrace comprehensive analyses by nine competent chemists whose results were in many cases checked by physiologic tests. The findings demonstrate beyond reasonable doubt or contradiction that there is no *potent ingredient in Wine of Cardui except alcohol.* The preparation is, therefore, *absolutely worthless* for the treatment of any condition in which 20 per cent. alcohol would not be indicated. That the results obtained in the analyses of Wine of Cardui by the several chemists are substantially correct was admitted by the manufacturer's chemist, Dr. Charles E. Caspari, in a recent trial (*Patten* vs. *American Medical Association*) in the Federal Court at Chicago before Judge Carpenter. A portion of Dr. Caspari's testimony follows as transcribed from the record:

Mr. Hough (for the plaintiff):—*Q.* Have you ever analyzed Wine of Cardui for the purpose of determining the percentage of alcohol present?

Witness (for the plaintiff): *A.* I have.

Q.—What did you ascertain?

A.—Between nineteen and a half to twenty per cent. by volume.

Q.—Have you ever attempted to analyze Wine of Cardui for the purpose of ascertaining the ingredients from which it was made?

A.—I have.

Q.—Other than the alcohol?

A.—I have.

Q.—Could you ascertain?

A.—I could not.

Q.—Now, what were the results of your analysis?

A.—My results were practically the same as those that have been obtained by all the chemists who have testified in this case, up to the present time. [The chemists who had testified in the case up to that time were Dr. Webster, Dr. McAbee, Dr. Hilpert, Dr. Leech, Professor Clark, Professor Stevens, Mr. Warren, and Dr. Loevenhart.—Ed.]

The reports from the several analysts are given in full in the succeeding pages.

REPORT ON THE ANALYSES OF WINE OF CARDUI

BY

L. E. Warren, Ph.C., B.S.

On Oct. 11, 1913, I received from Dr. A. J. Cramp of the Propaganda department of the American Medical Association a specimen said to be Wine of Cardui. The printed labels had been removed from the package and an American Medical Association stick label attached which bore the statement, in Dr. Cramp's handwriting:

"WINE OF CARDUI PURCHASED OCT. 11, 1913, BY A. J. CRAMP."

The stick label bore the Propaganda department's serial number 7796. I marked this label with my name, and later, when I sealed the bottle, with statement to that effect.

The specimen was a dark brownish to brownish-red liquid containing a little sediment, having a neutral reaction, a peculiar, valerian-like odor and a bitter, somewhat mawkish taste.

According to the labels of the package, the preparation is claimed to be "a purely vegetable extract," and the presence of 20 per cent. of alcohol by volume is declared. * Alcohol was determined, and 20.36 per cent. of absolute alcohol by volume was found. The distillate obtained in the alcohol determination was perfectly clear and, although it had a noticeable valerian-like odor, further dilution with water caused no turbidity, thus indicating absence (unless in minute traces) of volatile oils or of oleoresins. The absence of more than traces of extractives from a large number of drugs (the volatile oil-bearing drugs) was thus demonstrated.

The ash amounted to 0.666 gm. per hundred c.c. of material. The ash had an alkaline reaction and contained aluminum, calcium, magnesium, potassium and sodium salts, most of which appeared to be in the form of carbonates. A trace of iron was found. In short, the ash appeared to be such as would be expected to be obtained from plant extractives. The small quantity of ash excluded from the preparation, at least in therapeutically effective quantities, the presence of

such purgative salts as magnesium citrate, magnesium sulphate or potassium sodium tartrate.

The residue on evaporation amounted to 3.31 gm. per hundred c.c. It was a reddish-brown, slightly hygroscopic solid having a molasses-like odor. Its taste was similar to that of Wine of Cardui except for the absence of the taste of alcohol. It dissolved in water to form a turbid solution. It contained small amounts of copper-reducing substances, of nitrates and a trace of tannin but no glycerin. A trace of ammonia was present. Arsenic, antimony and mercury compounds, bromids, iodids, phenolphthalein, benzoates, salicylates, the potent alkaloids, such as aconitin, morphin and strychnin, and the emodin-bearing drugs, such as aloes, buckthorn, cascara, rhubarb and senna were absent.

The odor of the preparation was not winelike in any particular, and careful tests for tartrates and succinates gave negative results. The high alcohol content, the absence of acidity, of glycerin, of tartrates, of succinates, and of a winelike odor indicated that the preparation was not a wine in any sense of the term. In my opinion the name "Wine of Cardui," therefore, is false and misleading.

On slight acidification of the filtered, dealcoholized specimen with hydrochloric acid, a slight, flocculent precipitate was obtained. This was filtered off and dissolved in ammonia water, to form a dark brown solution. On evaporation of this solution a brownish-black, tasteless residue remained which could not be identified. It was probably apothem. Glycyrrhiza was thus proved absent, and appreciable quantities of resin-containing drugs, such as jalap, podophyllum and scammony, likewise excluded. A minute trace of material giving the reactions for alkaloids was extracted by ether from the dealcoholized material after making alkaline with ammonia. It was present in such minute traces that in the first analysis no attempt was made to purify or identify it. [It was later shown by the application of more refined analytic methods that no alkaloids were present.]

The dealcoholized, slightly acidified preparation was shaken successively with ether and chloroform. Small quantities of residues were given which tasted like the residues obtained from extracts from known blessed thistle after similar treatment. These residues could not be identified by the methods described in Fuller's "The Qualitative Analysis of Medicinal Preparations."

From a comparison of the extractives obtained from blessed thistle with those obtained from Wine of Cardui, it was concluded that Wine of Cardui probably is a hydro-alcoholic solution of the extractives from blessed thistle with perhaps a trace of valerian added. [It is now believed that the valerian-like odor comes from small amounts of black haw.] From the negative evidence obtained in the chemical examination, it is believed that Wine of Cardui contains no potent substances other than alcohol, unless they be present in minute traces.

Based on the foregoing analysis, an abstract of the analytic report was published in *The Journal of the American Medical Association,* April 11, 1914, as follows:

"The name Wine of Cardui would indicate that the preparation was made from blessed cardus (Cnicus benedictus), a plant variously known as blessed, cursed, spotted or bitter thistle. Wine of Cardui is a dark brownish liquid having a neutral reaction, a peculiar valerian-like odor and a bitter, mawkish taste. The odor was not wine-like in any particular. The preparation is claimed to be purely vegetable and the presence of 20 per cent. of alcohol is declared. Arsenic, bromids, iodids, the potent alkaloids such as aconitin, morphin and strychnin, or the emodin-bearing drugs, such as aloes, cascara and senna, were not found. Potassium bitartrate (cream of tartar) was absent, thus indicating the absence of wine from grapes. Alcohol was determined and 20.36 per cent. of absolute alcohol by volume was found. The volatile matter amounted to about 97 per cent. The nonvolatile residue appeared to consist of vegetable extractives. This had a bitter taste and gave very faint reactions for alkaloids. The quantity of alkaloid was too small to possess any appreciable medicinal effect, whatever its potency might be. Small quantities of a nitrate were present. Potassium nitrate is a constituent of a considerable number of plants, among which is blessed thistle. The presence of traces of this salt in Wine of Cardui does not, therefore, prove the presence of blessed thistle extractives in this preparation, although it is confirmatory evidence. A trace of combined ammonia also was present.

"It is probable that Wine of Cardui is a weak, hydro-alcoholic extract of blessed thistle, containing a trace of valerian. Blessed thistle has been employed to some extent in domestic medicine as a simple bitter, but little attention is given to it by discriminating writers in materia medica. It seems probable that whatever medicinal effect Wine of Cardui may possess is due principally to its alcohol content."

After the foregoing abstract had been published, a second specimen of Wine of Cardui was examined. This was purchased by me on May 25, 1914, of Mr. William Kuehn, a pharmacist whose store is at Garfield and Seminary Avenues, Chicago. He did not have a specimen in stock when first called on but, according to his statement, procured one of

a brother pharmacist whose store was not far off. The package was taken by me on the day after purchase to the Propaganda department where it was given the serial number 8930. To judge from the label of the preparation it had probably been manufactured before the Food and Drugs Act of June 30, 1906, came into force. In general, the specimen resembled the one previously examined, but it had no valerian-like odor. On evaporation it gave an average of 3.09 gm. of solids per hundred c.c. and contained 22.40 per cent. of alcohol by volume. As the specimen appeared to be an old one an exhaustive analysis of it was not made. So far as the examination was carried out no potent substances other than alcohol were found in the specimen.

Another specimen of Wine of Cardui was then obtained. This was purchased on the open market, June 13, 1914, in Chicago. It was given the serial number 8953. The specimen was then subjected to examination. The preparation was a dark brownish to brownish-red liquid containing some sediment and having a valerian-like odor, and a bitter, mawkish taste. The specific gravity was 0.99402 at 15.6 C. The reaction was very faintly acid to litmus. The preparation contained 19.81 per cent. of alcohol by volume, on evaporation gave 2.75 gm. of solids per hundred c.c., and on being burned gave 0.760 gm. of ash per hundred c.c. of material. The ash had an alkaline reaction and consisted of small amounts of the salts of sodium, calcium, potassium and magnesium with traces of aluminum and iron. Preliminary tests for alkaloids indicated their presence in small amounts, as in the first analysis, but confirmatory tests on purified residues were not carried out because the amounts of alkaloid indicated by the test (if present at all) were too minute to be of any importance. It was later shown by the application of more refined analytic methods that no alkaloids were present. The salts of arsenic, antimony and mercury, the purgative salts, such as magnesium sulphate (Epsom salt) or sodium sulphate (Glauber's salt), the emodin-bearing drugs, such as cascara, senna or rhubarb, the bromids, the iodids, tartrates and glycerin were absent. Small amounts of reducing substances, and of a nitrate, probably potassium nitrate, and a trace of combined ammonia were found. The absence in appreciable amounts of drugs usually accredited with emetic properties, such as ipecac, lobelia and tobacco, was established by chemical tests and also by physiologic experiments on human beings. The physiologic tests

consisted in swallowing large doses of the preparation which had been dealcoholized, and noting whether emesis or nausea took place; also in making ether extracts of the dealcoholized preparation and swallowing these. No nausea or emesis was noted. No untoward effect whatever was observed. The results of the analysis and physiologic tests prove beyond doubt that Wine of Cardui contains no potent ingredients in appreciable quantities other than alcohol. Based on this confirmatory analysis, as well as by an analytic report from another chemist, the abstract of the analytic report was again published in *The Journal of the American Medical Association,* July 18, 1914.

In the autumn of 1915 another analysis of Wine of Cardui was made. This specimen consisted of a mixture of the contents of four bottles of the preparation which had been purchased of the High-King Drug Company, Columbus, Ohio. They were received, June 20, 1914. The laboratory numbers of these bottles were 9945, 9946, 9947 and 9948. The mixed specimen was a dark brownish-red liquid having a valerian-like, but not winelike odor, a bitter, mawkish taste and containing a little suspended matter. Purgative salts, the salts of antimony, arsenic and mercury, alkaloids, benzoates, citrates, salicylates, succinates, tartrates, emodin-bearing drugs, glycerin, bromids and iodids were absent. Volatile oils (except possibly in the most minute traces) were absent. Small quantities of caramel and ammonium salts and traces of a nitrate and of tannin were present. No potent substances except alcohol were found in any appreciable quantities.

The following quantitative values were found:

Specific gravity at 15.6 C.	0.9902	
Alcohol	19.73	per cent. by volume
Solids	2.69	gm. per hundred c.c.
Ash	0.81	gm. per hundred c.c.
Suspended matter	0.036	gm. per hundred c.c.
Acid-precipitable	0.066	gm. per hundred c.c.
Resinous substances (by Stas-Otto method).	0.006	gm. per hundred c.c.
Alcohol-precipitable	0.257	gm. per hundred c.c.
Copper-reducing substances (usually calculated as dextrose)	0.613	gm. per hundred c.c.
Total nitrogen	0.046	gm. per hundred c.c.

The presence of black haw having been suspected in Wine of Cardui, an attempt was made to estimate its quantity by a determination of resins in the preparation (Wine of Cardui) as compared with a fluidextract of black haw of authentic origin.

The U. S. P. VIII prescribes a method for making fluidextract of black haw from the official drug (which is the bark of the root of *Viburnum prunifolium*). The U. S. P. of 1890 also prescribed a method for making a fluidextract of the drug official in that work which was the bark of the stem. A fluidextract of *Viburnum prunifolium* was prepared from an authenticated specimen of the bark of the stem of *Viburnum prunifolium*, the method prescribed by the U. S. P. of 1890 being used. The resins in 20 c.c. (ten doses) of this preparation were determined by the Stas-Otto method. In ten doses of the fluidextract, 0.7954 gm. of resin was found, or 0.07954 gm. per dose. The resins (or substances obtained by the Stas-Otto method where resins would be expected) in ten doses (160 c.c.) of Wine of Cardui were also determined. From ten doses of the preparation 0.0101 gm. of acid precipitable substance was found, or 0.00101 gm. for each dose. Hence one dose of the laboratory specimen of fluidextract of *Viburnum prunifolium* contains 78.75 times as much resin as does one dose of Wine of Cardui. In other words, if the resins be taken as a criterion, one dose of Wine of Cardui contains not more than one seventy-ninth of an official dose of viburnum. The absence of more than traces of resins excludes the presence of jalap, scammony and podophyllum.

The results of the analysis in a general way confirm the findings of the previous analyses and demonstrate the absence of potent drugs—except alcohol—in Wine of Cardui, at least in appreciable quantities.

Details of Analysis

Specific Gravity.—The specific gravity of a specimen of material was determined by a pycnometer and found to be 0.9940 at $\frac{15.6\ C.}{15.6\ C.}$.

Residue on Drying.—A portion of the liquid was evaporated in a weighed beaker on a water bath and the residue dried at 100 C. The residue from 10 c.c. weighed 0.3314 gm., equivalent to 3.314 gm. in 100 c.c. of material. A determination was later made on a portion of another specimen. The residue from 10 c.c. weighed 0.3143 gm., equivalent to 3.143 gm. in each 100 c.c. A duplicate gave 0.3042 gm., equivalent to 3.042 gm. per hundred c.c., average 3.09 gm. per hundred c.c. Still later other specimens gave residues amounting, respectively, to 2.75 and 2.69 gm. per hundred c.c.

At another time the contents of an entire bottle (260 c.c.) were evaporated, the residue dried and weighed as described above. The residue weighed 7.6468 gm., equivalent to 2.94 gm. per hundred c.c.

Ash.—Ash was first determined by evaporating a measured portion to dryness and heating the residue in a porcelain dish until no further loss in weight was noted. Later it was found best to first heat the dried residue until charred. The mass was then cooled, leached with water on an ash free filter, the filter dried, burned, the leachings added to the residue of ash, the whole evaporated to dryness, and the residue dried and again heated, at low redness, to constant weight. The ash from 10 c.c. weighed 0.0666 gm., equivalent to 0.6660 gm. per hundred c.c. Other specimens gave ash equivalent to 0.76 and 0.81 gm. per hundred c.c. The reaction of the ash was alkaline to litmus. The small quantity of ash excluded such purgative salts as magnesium citrate, magnesium sulphate and potassium sodium tartrate in medicinal amounts.

Metals, etc.—The absence of antimony, arsenic, bromids and iodids and of copper and zinc salts was demonstrated by the usual tests. To 25 c.c. of the material a few drops of 10 per cent. sodium hydroxid solution were added, the solution evaporated to dryness, the residue charred, the mass cooled, leached with water, the leachings acidulated with hydrochloric acid, and the usual tests applied to the filtrate. A trace of iron was found. Mercury was tested for by hydrogen sulphid in the original solution after evaporation of the alcohol, acidifying and filtering, but none was found.

Alcohol.—This was determined by the provisional method of the Association of Official Agricultural Chemists.[10] The specific gravity of the distillate (100 c.c. diluted and distilled to 100 c.c.) was 0.97572 at $\frac{15.6\ C.}{15.6\ C.}$ corresponding to 20.36 per cent. of absolute alcohol by volume. The alcohol content of other specimens was found by this method to be, respectively, 22.40, 19.81 and 19.73 per cent. by volume.

Alkaloids.—A portion of the material was dealcoholized by dilution with water and subsequent evaporation. The residue was made alkaline with ammonia water and shaken with several successive portions of ether. The solvent was allowed partially to evaporate spontaneously, the ethereal

10. Bull. 107, Bureau of Chemistry, p. 83.

solution shaken with very dilute hydrochloric acid, and the acid solution made alkaline with ammonia water and shaken with chloroform. The solvent was evaporated, the residue taken up in warm, very dilute hydrochloric acid, the solution filtered, and the usual alkaloidal reagents applied to portions of the filtrate. A faint cloudiness appeared after some time. Only minute traces of alkaloid were thus indicated. In later tests the solution at this stage was precipitated with iodin solution, the mixture allowed to stand over night, the precipitate washed with water and decomposed on the filter with a few drops of sodium thiosulphate solution, and the filtrate was passed several times through the filter, after which it was made alkaline with ammonia water and shaken with chloroform. The solvent was evaporated, the residue taken up in a few drops of very dilute hydrochloric acid, and the usual alkaloidal reagents, such as mercuric potassium iodid, iodin solution, picric acid, etc., added. No cloudiness or precipitation was given, indicating absence of alkaloids. The tests were carried out on 25 c.c., 50 c.c., 100 c.c. and 271 c.c. (one bottle) portions of the material. The absence of more than the most minute traces of such physiologically active drugs as aconite, belladonna, cinchona, opium and nux vomica was thus demonstrated; also the absence of more than the most minute traces of such emetic drugs as apomorphin, ipecac, lobelia, physostigma, pilocarpus and tobacco was demonstrated. One specimen (out of five tested) did not give any preliminary tests for alkaloids.

In order to determine whether any substances were present in Wine of Cardui which would interfere with the extraction of alkaloids, a control was carried out as follows:

After the extraction of the 271 c.c. portion had been completed, a quantity of strychnin hydrochlorid, equivalent to 0.0005 gm. of alkaloid, was added to the residue in the separator, and the extraction and purification processes repeated as described above.

Abundant and satisfactory tests for alkaloids were obtained in the resultant acid solutions with the usual alkaloidal reagents, and portions of the dried chloroform extract gave the "fading purple" test for strychnin. This shows that less than $\frac{1}{100}$ grain of strychnin in an entire bottle of Wine of Cardui may be detected readily and positively. Consequently no substance which interferes with the detection of alkaloids is present in appreciable amounts in Wine of Cardui.

Emodin-Bearing Drugs.—These were tested for by Borntraeger's method.[11] Briefly, the method consists in shaking the dealcoholized, slightly acidified extract of the drug with benzene (benzol, C_6H_6), washing the benzene solution first with water which is discarded and then with very dilute ammonia water. If emodin or other anthraquinone compounds (or phenolphthalein) be present the ammoniacal layer becomes red, the depth of color and shade depending somewhat on the amount of anthraquinone compound (or phenolphthalein) present and the drug from which obtained. The results were negative. Therefore, such purgative drugs as aloes, buckthorn, cascara, phenolphthalein, rhubarb and senna are absent, at least in quantities more than traces.

Salicylates.—A portion of the dealcoholized, acidified preparation was extracted with ether, the solvent evaporated, the residue taken up in warm water so far as possible, the solution filtered, and ferric chlorid solution added to a portion of the filtrate. A violet color was not produced.

Benzoates and Succinates.—A portion of the aqueous filtrate obtained from the ether extract as a preliminary in the test for salicylates was made alkaline with ammonia water, the mixture evaporated to dryness, the residue taken up with water, and the solution treated with neutral ferric chlorid solution. Neither a flesh-colored precipitate nor a cinnamon-brown precipitate was produced.

Potassium Bitartrate.—The material had a neutral reaction, thus indicating the probable absence of potassium bitartrate and, hence, of wine from grapes. The alcohol was removed from 100 c.c. of the material by dilution with water and evaporation. To the residue an excess of basic lead acetate solution was added, the resultant precipitate collected, washed with water, suspended in water, and hydrogen sulphid passed in until no further precipitation took place. The lead sulphid was removed by filtration, and the filtrate evaporated nearly to dryness. The residue had a strong reaction but did not give tests for tartaric acid when portions of the solution were subjected to the following tests:

If a drop of ferrous sulphate solution be added to a solution of tartaric acid or a soluble tartrate, a few drops of hydrogen peroxid solution added and the mixture finally treated with excess of sodium hydroxid solution, a fine violet coloration is produced, which, in strong solution of tartrate, is so deep as to appear almost black.

11. Borntraeger: Ztschr. anal. Chem., 1880, **19**, 165.

If a concentrated solution of tartaric acid be mixed with a concentrated solution of potassium acetate, a white crystalline precipitate of potassium bitartrate should be produced.

If a solution of tartaric acid be just neutralized with calcium hydroxid solution, the precipitate if any removed by filtration, the filtrate warmed and allowed to stand over night, a crystalline deposit of calcium tartrate should be formed.

Citrates.—A portion of the resultant acid solution obtained as a preliminary in the test for tartrates was tested for citric acid by Denige's test with negative results. The test was carried out as follows:

About 1 gm. of mercuric oxid is dissolved in 25 c.c. of 35 per cent. sulphuric acid. About 1 c.c. of the reagent is added to about 5 c.c. of the suspected citric acid solution, the mixture heated to boiling and a few drops of tenth-normal potassium permanganate added. If citric acid or citrate be present a white precipitate should be produced.

Suspended Matter.—As the preparation was not clear, a portion was filtered through a weighed Gooch crucible, the residue washed with 10 c.c. of water, dried at 100 C. and weighed. From 100 c.c. of the material a residue of 0.0367 gm. was obtained. A duplicate gave 0.0354 gm.; average, 0.0361 gm. of suspended matter per hundred c.c. of material.

Acid-Precipitable Substances.—The filtrate from the determination of "suspended matter" was evaporated to remove alcohol, the solution acidified with hydrochloric acid, diluted with water to original volume, the solution allowed to stand for twenty-four hours, the precipitate collected in a weighed Gooch crucible, the precipitate dried at 100 C., and weighed. From 100 c.c. of the original material a precipitate weighing 0.0687 gm. was obtained. A duplicate gave 0.0634 gm. of precipitate, average, 0.066 gm. per hundred c.c. The residue dissolved in ammonia water to form a dark brown solution. On evaporation of the solution a brownish-black, tasteless residue remained which could not be identified. Glycyrrhiza was thus proved absent, as were also appreciable quantities of resin-containing drugs, such as podophyllum, jalap and scammony. The acid-precipitable substance is probably apothem.

Blessed Thistle.—The dealcoholized slightly acidified specimens of Wine of Cardui were shaken successively with ether and chloroform; on subsequent evaporation of the solvents, small quantities of residues were given which tasted like the residues obtained from extracts of authenticated blessed thistle after similar treatment. These residues could not be

identified by the methods described in Fuller's "The Qualitative Analysis of Medicinal Preparations." Since their taste and general appearance were so similar to extracts from blessed thistle, it seemed reasonable to conclude that blessed thistle is present in Wine of Cardui.

Alcohol-Precipitable Substances.—To the filtrate from the suspended matter (110 c.c.), 440 c.c. of alcohol were added and the mixture allowed to stand over night. The precipitate was collected in a weighed Gooch crucible, washed with about 10 c.c. of 75 per cent. alcohol, dried at 100 C. for one hour, and weighed. From 100 c.c. of material, 0.2595 gm. of precipitate was obtained. A duplicate gave 0.2546 gm. of precipitate. Average, 0.2571 gm. of alcohol-precipitable substances per hundred c.c. of material.

Nitrates.—A portion of the dealcoholized material was acidified with hydrochloric acid, the resultant precipitate removed by filtration, and the well known diphenylamin test for nitrates applied to a portion of the filtrate. A positive reaction was obtained.

Total Nitrogen.—Nitrogen was determined by the Gunning method as modified for nitrates.[12] The mixture foamed badly so that it was found necessary to use much care in the digestion. The ammonia obtained from 100 c.c. of material consumed 3.279 c.c. of normal sulphuric acid, equivalent to 0.04567 gm. of nitrogen.

Physiologic Tests.—For the physiologic tests the alcohol was removed from 75 c.c. of the material by placing in a 250 c.c. beaker, evaporating on the steam bath to a volume of about 30 c.c., diluting the residue with 25 c.c. of water, and evaporating this mixture to about 25 c.c. The mixture was then cooled, shaken and swallowed, the beaker being washed with a little water and the washings also swallowed. In the test in which the contents of an entire bottle were taken at a single dose, the method was essentially the same as described above except that a larger beaker (600 c.c.) was used for the evaporation, the final volume of solution in this test being 132 c.c. The blood pressure, pulse and temperature were observed by a physician both before and after the material was swallowed. No changes worthy of note occurred.

In another physiologic test the alcohol from the contents of an entire bottle was removed as described above and the residue shaken four times with 50 c.c. each of ether.

12. Bull. 103, Bureau of Chemistry, p. 8.

The solution was then made slightly alkaline with ammonia water and shaken four times with 50 c.c. each of ether. The ethereal solutions were united, allowed to evaporate spontaneously, the residue taken up in a little alcohol, and the solution made into a thick paste with lactose. The alcohol was allowed to evaporate spontaneously from the mixture and the residue put into capsules. About three eighths of the capsules were taken at one dose and the remainder on the following day. No results except a very slight belching of gas were observed.

Other tests consisted in swallowing five doses of the preparation from which the alcohol had not been removed and which had not been subjected to any physical or chemical treatment. The preparation was swallowed at 8 p. m., an hour after a light dinner. A feeling of warmth in the throat and stomach was noted at once. After from fifteen to twenty minutes some flushing of the face was noted, and in about thirty minutes a feeling of exhilaration. About sixty minutes after the preparation had been swallowed, a sensation of fulness of the head was noted followed by a slight headache which lasted until sleep came on, or until about 10:30 p. m. There was a slight belching of gas from the stomach at one period of the experiment, but no nausea was experienced at any time. The following evening 75 c.c. of 20.42 per cent. alcohol was swallowed. The symptoms in all respects were similar to those obtained after swallowing Wine of Cardui.

CHEMICAL EXAMINATION OF WINE OF CARDUI

BY

Paul Nicholas Leech, Ph.D.

A chemical examination of Wine of Cardui was undertaken in February, 1915, with two points in view:

1. To make a general examination which would show the presence or absence of potent drugs and to determine quantitatively certain analytic factors in order to ascertain how nearly they corroborated the results of other chemists.

2. To determine, if possible, (*a*) a synthetic method for preparing "Wine of Cardui," and then subjecting it and other preparations made with a modification of the formula to the same parallel examination as the commercial specimen of

Wine of Cardui; (*b*) the amount of volatile oil in Wine of Cardui; (*c*) the comparative amount of valerate radical.

All the specimens examined were bought on the market, either in Chicago or elsewhere. According to the label, "Wine of Cardui or Woman's Relief" is manufactured by the Chattanooga Medicine Co., Chattanooga, Tenn., and "is recommended for all irregularities of the menstrual functions (except when caused by malformation, or diseases requiring surgical treatment)." The daily dose, according to the directions, is a maximum of 4 tablespoonfuls (64 c.c.). The presence of 20 per cent. alcohol, by volume, is declared.

I

GENERAL ANALYSIS

The contents of four bottles, after thorough mixing, were used for the quantitative work except for the iron determinations. The bottles contained a brown, murky liquid, very slightly acid, and having some insoluble organic matter present. The liquid had an odor of valerian, and a bitter and rather unpleasant taste. Qualitative tests demonstrated the absence of alkaloids;[13] this proved the absence of a considerable number of potent drugs.

Arsenic, antimony and mercury were absent. The small amount of ash also disclaimed the presence of many inorganic compounds in such amounts as to be appreciably therapeutically active. The ash gave tests for iron, calcium, magnesium, sodium and potassium, but no other metals; chlorid, carbonate and nitrate were present.

Emodin-bearing drugs or aloin were not found to be present. Iodids and bromids were absent. Yeast cells were present. Precipitation was caused by the addition of acid. Lead acetate gave a precipitate.

A small amount of reducing sugar was present, but was not determined. Caramel was identified.

Glycerin was not found to be present in Wine of Cardui. One hundred c.c. of Wine of Cardui were treated with lime, etc., according to the glycerin determination described in

13. With the usual method of purification, repeated shaking out with acidified water, etc., the material responded to tests with KI_3 and Mayer's reagent for alkaloids, but indicated only an extremely small amount. The substance, however, was not an alkaloid, as was demonstrated by following out the method, described by Warren (see this report, p. 52).

McELREE'S

WINE OF CARDUI

OR

WOMAN'S RELIEF

CONTAINS 20 PER CENT. ALCOHOL

Chattanooga Medicine Co.

Proprietors & Manufacturers

CHATTANOOGA, TENN.

THE ALCOHOL (ABOUT 16 3/5 PER CENT. BY WEIGHT) IS USED AS A SOLVENT AND PRESERVATIVE OF THE ACTIVE MEDICINAL INGREDIENTS.

DIRECTIONS

DOSE—A TABLESPOONFUL.

AS A TONIC, TAKE A DOSE THREE TIMES A DAY.

FOR IRREGULAR, PAINFUL OR DELAYED MENSTRUATION, A DOSE THREE TIMES A DAY.

FOR PROFUSE OR TOO FREQUENT FLOW, A DOSE THREE TO FOUR TIMES A DAY DURING PERIOD; THEN TWO DOSES A DAY UNTIL THE NEXT PERIOD, WHEN INCREASE TO THREE AND FOUR DOSES AS BEFORE.

FOR ENTIRE SUPPRESSION, TAKE A DOSE 4 TIMES A DAY.

NOTE. SEE FURTHER DIRECTIONS ON CIRCULAR ENCLOSED. KEEP BOWELS REGULAR WITH THEDFORD'S BLACK-DRAUGHT.

GUARANTEED BY
Chattanooga Medicine Co.
Under the Food & Drugs Act, June 30, 1906.
No. A. 171.

McELREE'S

WINE OF CARDUI

OR

WOMAN'S RELIEF

KEEP WELL CORKED

This Medicine is a purely vegetable extract, and has proven to be a reliable Remedy For the Treatment of Female Diseases

It is recommended for all irregularities of the menstrual functions, (except when caused by malformation, or diseases requiring surgical treatment), especially for Suppressed or Delayed Menses, Painful Menstruation, Profuse or too Frequent Flow of Menses, Whites, Falling of the Womb, Change of Life, and as a general Restorative for Delicate Women.

SHAKE THE BOTTLE

Chattanooga Medicine Co.
Chattanooga, Tenn.

SOLE MANUFACTURERS
—AND—
PROPRIETORS.

Bottle labels used after the Food and Drugs Act became effective.

"Food Inspection and Analysis."[14] A small amount of a viscous extract was obtained (not glycerin) which had a celery-like odor, and solidified at about 30 C. Whether or not this was due to a constituent of *Carduus benedictus* was not determined.

The presence of *Carduus benedictus*[15] (*Cnicus benedictus,* blessed thistle) was suspected, owing to the similarity of name (Cardui) and also to the presence of relatively large amounts of nitrate; therefore the herb itself was examined by means of the Stas-Otto and the Dragendorf methods of plant extraction. (The materials were first identified by a competent pharmacognocist). The odor of Wine of Cardui was such as would be derived from viburnum (prunifolium or opulus), valerian, or angelica. The viburnums are known to be constituents of many female proprietary remedies. Since *Viburnum opulus,* as bought on the market, is a spurious product, usually being *Acer spicatum,* it was tentatively presumed that *Viburnum prunifolium* was the cause of the valerian-like odor of Wine of Cardui, and experiments were devised accordingly.

Experiments were made with extractions with ligroin, ether and chloroform from both acid and alkaline solutions on Wine of Cardui, and extracts of *Carduus benedictus* and infusions of *Viburnum prunifolium.* The ether extract from the acid solution of Wine of Cardui gave a yellow "plate-like" substance, in considerable amount. *Carduus benedictus* also gave the same result. *Viburnum prunifolium* gave only traces of a bitter principle with these extractions. In physical properties, such as odor, taste, solubility in acid water, ligroin, chloroform, ether and acetone, refraction, appearance, etc., the yellow "plate-like" substances from Wine of Cardui and *Carduus benedictus,* respectively, were alike. The properties, as far as studied, were the same as those ascribed to Cnicin,[16] the bitter principle of *Carduus benedictus.*[17] The

14. Leach: Food Inspection and Analysis, revised by Winton, Ed. 3, p. 703.

15. In some old and uncritical medical literature, reference is found to the use of Carduus marianus, the seeds being used for tincture; Carduus benedictus is not to be confused with C. marianus. Tinctures made from C. benedictus (the stems and leaves being used) and C. marianus (the seeds being used) differed markedly in appearance, taste and odor.

16. Nativelle: Compt. rend. Acad. d. sc., 1842, **15,** 808. Schribe: Ibid., **15,** 802; Ann. Chem., 1842, **44,** 289. Schwander: Dissertation, Botan. Centralbl., Beihefte, 1894, p. 527.

17. There was no substance in the extract of the seeds of Carduus marianus which was similar to cnicin.

chloroform fraction (from alkaline solution) of the *Viburnum prunifolium* yielded a minute trace of an alkaloidal reacting substance. Viburnum infusion readily gave a red color with alkali. Wine of Cardui did the same, but carduus extract did not. Nitrate was present in both Wine of Cardui and extract of carduus.

Wine of Cardui (500 c.c.) was subjected to steam distillation until about 400 c.c. of distillate were collected; the contents in the distillation flask were then acidified with sulphuric acid, and steam again passed through. Careful extraction of the first distillate with ether yielded a very small amount of a substance which had a predominating odor of valerian. When 500 c.c. of a tincture made from 10 per cent. *Carduus benedictus* and 10 per cent. *Viburnum prunifolium* were tested as above, a similar residue was observed, but in greater amount. In other respects (such as nature of substance from acid distillation, appearance, odor, etc., of residual liquids) the experiments of the comparative distillations showed marked similarity. The foregoing work strongly indicated that *Carduus benedictus* and *Viburnum prunifolium*[18] entered into the make-up of Wine of Cardui. Accordingly it was decided to attempt to synthesize a preparation, having the same qualities as Wine of Cardui—chemically—and giving the same quantitative data. This phase will be discussed later.

So far the only therapeutically potent ingredient found besides the alcohol was iron. Therefore an iron determination was made, along with other following quantitative data.

Specific gravity at 15.6 C.....	0.9932	
Alcohol (by volume).....	19.33	per cent.
Solids (by weight).....	3.44	per cent.
Ash	0.75	per cent.
Alkalinity of ash.....	9.38	c.c. normal alkali
Iron	0.0006	per cent.
Potassium (calculated as potassium carbonate).....	0.57	per cent.
Sodium (calculated as sodium carbonate)	0.24	per cent.

Each of the iron determinations was made on the entire contents of two original bottles of Wine of Cardui. After proper treatment, the iron was determined by titration with

18. At one stage, it was thought that apiol might be a constituent of Wine of Cardui. This, however, was subsequently disproved.

potassium permanganate solution. *From the result obtained, it would take 10,000 c.c. (2⅔ gallons) of Wine of Cardui to yield one therapeutic dose of iron* (0.06 gm. or 1 grain).

PHYSIOLOGIC TESTS

Since the foregoing chemical examination did not reveal any potent constituents in Wine of Cardui except alcohol, it was decided to make a test by drinking some Wine of Cardui. Three persons (including the writer) each swallowed at one dose 64 c.c. of Wine of Cardui. Each subject reported no effect other than that due to alcohol, such as a feeling of warmth in the stomach, flushing of face and slight "headiness." Otherwise all felt normal both on the day of administration and on the following day. In none did it produce either emesis or even nausea. In order to compare the action of Wine of Cardui, 64 c.c. of a 20 per cent solution of alcohol were taken a few days later. The reactions experienced were similar to those of Wine of Cardui. In two instances the experimenters experienced more difficulty in drinking the alcohol solution than the bitter Wine of Cardui both containing the same amount of alcohol. These experiments further substantiate the absence of physiologically active drugs other than the alcohol. The experiments also disprove the presence of an emetic, which principle the manufacturers, through their attorneys, stated to be in Wine of Cardui.

II

SYNTHETIC PREPARATIONS

Imitations of Wine of Cardui were attempted, with the aim of making a preparation which, when subjected to the same qualitative and quantitative tests as Wine of Cardui itself, would give concordant results. If such a preparation could be obtained, it would be safe to state that the ingredients (and their quantitative relations) which were corporated into such a preparation would be essentially the same as those in Wine of Cardui. Hence numerous attempts were made with the employment of various methods, such as making water infusions, then adding alcohol to the concentration of 20 per cent. by volume; making alkali infusion and adding alcohol, percolating with 95 per cent. alcohol, then diluting, percolating with 20 per cent. alcohol and in instances adding alkali, etc. At first the drugs used were *Carduus benedictus*

(No. 40 powder) and *Viburnum prunifolium* (No. 40 powder) in different proportions. The solutions stood about two months. Those prepared with potassium hydroxid or sodium hydroxid turned black and had a rather weak odor, whereas the ones in which sodium carbonate was employed did not turn black. The latter also gave a heavy precipitate from an alcoholic percolate. The odor of valerian developed markedly on standing. In all the experiments, the *Carduus benedictus* was used in a much greater proportion than the *Viburnum prunifolium* (black haw). Checks were made with Wine of Cardui. At about this time, an article by Robert C. Bicknel, formerly chemist for the Chattanooga Medicine Company, appeared in *Harper's Weekly* for Oct. 23, 1915. A "report on a mess of 'Wine of Cardui'" gave the following figures:

CARDUI

Amount, 300 gal.

Materials		Amount
Cardui Herb "A"	300 lbs.	..... oz.
Cardui Herb "B"	... lbs.	..... oz.
Cardui Herb "C"	... lbs.	..... oz.
B. H.	30 lbs.	..... oz.
Alcohol	64 gal.	..... oz.
Sod. carbonate	6^{15} lbs.	..... oz.
Caramel āā q. s.	10 lbs.	..... oz.

In the same article, Bicknel also made the following statements:

"Besides alcohol and water, the 'Wine of Cardui,' previous to 1906, contained the herb *Carduus benedictus*, or blessed thistle, in the proportion of one pound to the gallon. Caramel, or burnt sugar, was added for coloring purposes, when necessary, and a small amount of sodium carbonate, to make the mixture settle clear. That was all.

"Just before the Food and Drugs Act went into effect, a small amount of black haw bark, equal to 10 per cent. of the carduus herb used (i. e., 1.6 ounces to the gallon) was added to the formula. No other changes were made."

Although the formula was somewhat confusing, yet the general quantities given were used. The resulting preparations, when made with the whole *Carduus benedictus* herb and ground *Viburnum prunifolium* (bark of the stem), closely resembled Wine of Cardui in its physical properties, but yielded lower quantitative data than with Wine of Cardui. The next step was to increase the amount of the drugs. Considering the viburnum to be 10 per cent. of the total herbs, the next amounts taken were in the ratio of 315 parts of

Carduus benedictus (whole crushed stem, leaves and fruit) and 35 parts *Viburnum prunifolium* (bark of stem ground) to make 300 parts (in terms of gallons) of the preparation, some caramel and sodium carbonate being added. About this time information was received that Wine of Cardui was prepared by percolating 315 pounds of cardui herb (not chopped or ground) and 35 pounds of black haw (ground) with enough menstruum to make 300 gallons of the completed product. The menstruum was made by taking the washings from the previous tank after standing two hours and pumping into 68 gallons of alcohol (later 64 gallons with washings). The menstruum was run into the top of the percolator, and the contents allowed to macerate for twelve hours. In the "running down" process, the last of the menstruum was followed by water until the measure was completed. To the percolate was added 1 gallon of solution, containing 6 pounds of pure anhydrous sodium carbonate and 5 pounds of caramel. The tank was then allowed to stand one or two weeks, and decanted or bottled from above the sediment which has formed.

In the compounding of the various preparations, the following proportions were taken as a basis:

Divided by 300. Amt. in 1 gal.	C 315 lb.	V 35 lb.	Menstruum 300 gal.	95% alcohol 64 gal.	Na_2CO_3 6 lb.	Caram 5 lb.
	1.05 lb.	0.116 lb.	1 gal.	0.213 gal.	0.02 lb.	0.016 l
	||	||	||	||	||	||
	476.3 gm.	52.5 gm.	3.785.4 a	806.3 a	9.072 gm.	7.84 gn
Divided by 10	47.6	5.25	378.5	80.6	0.9	0.78

In the compounding of the preparations described below, however, three times the final amounts, or in other words one thousandth of the amount prescribed in the original figures were used, i. e., 142.8 gm. C., 15.75 gm. V.; 1,135.5 c.c. menstruum, 241.8 c.c. alcohol; 2.7 gm. anhydrous sodium carbonate; 2.34 gm. caramel.

A. Formula *A* was made as follows: In a percolator, 142.6 gm. of unchopped *Carduus benedictus* and 15.75 gm. of ground *Viburnum prunifolium* (bark of stem) were placed. Menstruum, made by diluting 241.8 c.c. of alcohol to 1,135 c.c. with water, was added, and the whole allowed to macerate for from fourteen to fifteen hours. The percolate was drawn off, and an extra amount of menstruum poured into the percolator, until the percolate drawn off had reached the original volume (1,135 c.c.). To the percolate were added

2.7 gm. of anhydrous sodium carbonate, and 2.3 gm. caramel, allowed to stand twelve days, and then filtered.

B. Formula *B* was made exactly as *A*, except that no caramel was used. Therefore it was made with alcohol, carduus, viburnum and sodium carbonate.

C. Formula *C* was made exactly as *A*, except that no viburnum was used. Therefore it was made with alcohol, carduus, caramel and sodium carbonate.

H. Formula *H* was made exactly as *A*, except that no viburnum or caramel was used. Therefore it was made with carduus, alcohol and sodium carbonate.

K. Formula *K* was made exactly as *A*, except that no carduus, caramel or sodium carbonate was used. Therefore it was made with viburnum and alcohol (20 per cent.).

In all the foregoing the same relative amounts were used. An extractive of carduus by 20 per cent. alcohol will give considerable precipitate with sodium carbonate.

These various preparations were submitted to qualitative and quantitative tests. Qualitatively Formula *A* behaved exactly as Wine of Cardui, and the tests also proved that the nitrate was from *Carduus benedictus*. Repeated parallel residue determinations were made, a typical series being as follows:

W. The amount of residue from 100 c.c. Wine of Cardui was 3.27 gm. The amount of residue from one dose (16 c.c.) of Wine of Cardui is equivalent to 0.52 gm.

A. The amount of residue from 100 c.c. of the extract, made according to Formula *A*, was 3.06 gm. The amount of residue from one dose (16 c.c.) is equivalent to 0.49 gm.

B. The amount of residue from 100 c.c. of the extract, made according to Formula *A*, but with the omission of caramel, was 2.50 gm. The amount of residue in one dose (16 c.c.) is equivalent to 0.40 gm.

C. The amount of residue from 100 c.c. of the extract made according to Formula *A*, but with the omission of the viburnum, was 2.36 gm.

H. The amount of residue from 100 c.c. of the extract made according to Formula *A*, but with the omission of viburnum and caramel, was 2.20 gm. The amount of residue from one dose (16 c.c.) is equivalent to 0.35 gm.

K. The amount of residue from 100 c.c. of the extract, made according to Formula *A*, but with the omission of

caramel, carduus and sodium carbonate, was 0.35 gm. The amount of residue (which is from *Viburnum prunifolium*, bark of stem) in one dose (16 c.c.) is equivalent to 0.06 gm.

X. The amount of residue from 100 c.c. of fluidextract of *Viburnum prunifolium* (bark of stem) was 25.21 gm. The amount of residue in one dose (2 c.c.) is equivalent to 0.51 gm.

Y. The amount of residue from 100 c.c. of fluidextract *Carduus benedictus* was 18.84 gm. The amount of residue in one dose (4 c.c.) is equivalent to 0.75 c.c.

Assuming that *Carduus benedictus* and *Viburnum prunifolium* actually had therapeutic value, and further assuming that the medicinal virtues[19] were extracted and remained in the residue, a comparison of the residue from Wine of Cardui with the residues from fluidextracts of either *Carduus benedictus* or *Viburnum prunifolium* showed the following: *In order to obtain a therapeutic dose of any of the drugs, the dose of Wine of Cardui would be so large that the quantity of alcohol administered would be much greater than if the fluidextracts themselves had been used.*

The foregoing preparations (Formulas *A, B, C, H* and *K*) were sent to Dr. Loevenhart of the University of Wisconsin for analysis. He reported as follows:

> "The five samples of 'synthetic' Wine of Cardui which were forwarded to me by the American Medical Association were subjected to analysis simultaneously together with a new specimen of Wine of Cardui purchased in the open market in Madison in order to have the figures as nearly comparable as possible. The enclosed table gives the result of these analyses. It would appear that Specimen *A* more closely approaches Wine of Cardui than the other specimens. The differences between Wine of Cardui and Specimen *A* are not striking. It should be noted that the specimen of Wine of Cardui here analyzed differs considerably from the specimen previously analyzed according to the results submitted in my first report. It should be pointed out that the determinations of nitrate calculated as potassium nitrate were colorimetric and are only approximate. It is interesting to note that the total nitrogen and the nitrate in these six specimens, including the (wine), run parallel; thus *K*, which contains no nitrate, also contains no nitrogen whatever, while *H*, which contains the most nitrogen, also contains the most nitrate."

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19. If the medicinal virtues are extracted, then on being dried, their virtue either remains in the residue, or is volatile. The volatile determination (see later) excludes any serious therapeutic consideration.

RESULTS OBTAINED IN THE ANALYSIS OF WINE OF CARDUI AND THE FIVE SYNTHETIC SPECIMENS
BY A. S. LOEVENHART

Substance Analyzed	Color	Taste	Odor	Turbidity	Reaction	Specific Gravity 22°	Total Solids, %	Ash, %	Reducing Material Calculated as Glucose, %	Total Nitrogen, %	Nitrate Calculated as KNO_3, %
W. Wine of Cardui	Murky brown	Bitter; also a slightly sweetish taste	.....	Turbid	Faintly alkaline to litmus	0.991	3.527	0.611	0.602	0.060	0.2
A. Carduus, viburnum, Na_2CO_3, caramel, alcohol	Murky brown	Very similar to W; sweetish taste less marked	Most like W; almost identical with it; possibly not quite as strong	Turbid	Definitely alkaline to litmus	0.994	3.252	0.797	0.250	0.104	0.3
B. Same as A, except no caramel added	More reddish; not so dark	Similar to W	Same as A and W; indistinguishable	Turbid	Same as A	0.9895	2.596	0.590	0.138	0.109	0.3
C. Same as A, except no viburnum added	Darker than B but lighter than A	Slightly bitter; not very much like W	Something like W; is similar to H	Clear	Same as A	0.989	2.397	0.756	0.105	0.117	0.6
H. Same as A, except no viburnum or caramel added	Lighter than B	Not much like W	Similar to C	Clear	Same as A	0.988	2.304	0.676	0.035	0.120	1.2
K. Same as A except no carduus, caramel or Na_2CO_3 used; only viburnum and alcohol	Reddish yellow; lightest of all	Nothing like W; not disagreeable; very slightly bitter; ester-like alcohol predominates	Entirely different from others; like alcohol and esters	Turbid	Neutral to litmus	0.975	0.358	0.017	0.054	0.000	0.0

COMMENT.—The viburnum contributes no nitrogen or nitrate; most of the glucose comes from the caramel. All analyses were done simultaneously. The nitrate determination is only approximate, but runs parallel to total nitrogen. Practically all nitrogen present is in the form of nitrate. The maximum nitrate which could have been present (from total nitrogen) was 0.866 per cent.

The directions for preparing Formula *A* were sent to Prof. A. H. Clark of the University of Illinois School of Pharmacy, and to Prof. A. B. Stevens of the University of Michigan. Both reported that the products prepared by them from Formula *A* and Wine of Cardui were similar (see page 78 and page 82).

FORMULA A

	Per Batch.	Per Gal.	Per Oz.	Per 1,135 c.c.	Per Cent. (Gm. per C.c.)
Carduus benedictus	315 lb.	1.05 lb.	57.43 grains	142.6 gm.	12.958%
Viburnum prunifolium	35 lb.	0.116 lb.	6.34 grains	15.75 gm.	1.429%
			(63.8)		
Na_2CO_3	6 lb.	0.02 lb.		2.7 gm.	0.245%
Caramel	5 lb.	0.016 lb.		2.3 gm.	0.204%
20 per cent. alcohol, q. s.....	300 gal.				

For the purpose of the Chattanooga trial (*Patten* v. *Dowling*), the attorneys for the plaintiff stated that one fluidounce of Wine of Cardui contained the extractives (20 per cent. alcohol being used) from 66 grains of combined blessed thistle and *Viburnum prunifolium* (bark of stem). In Formula *A*, the extractives are from 64 grains. At the Chicago trial, the hypothetic solution described for the consideration of the medical witnesses was assumed to contain the extractives in solution (20 per cent. alcohol being used) from 60 grains of *Carduus benedictus* and 6 grains of *Viburnum prunifolium* per fluidounce.

From these experiments it is safe to state that Wine of Cardui and Formula A, for all intents and purposes, are identical. The slight differences which exist are explainable by differences in samples of caramel and the drugs. Similar differences appear in different samples of the original Cardui.

VOLATILE MATTER

Small amounts of volatile matter have been ascribed to both *Carduus benedictus* and *Viburnum prunifolium*. It was thought, therefore, to be of interest to determine the relative amount of volatile matter (otherwise than alcohol and water) in Wine of Cardui. The measured contents of two bottles of Wine of Cardui were subjected to steam distillation. The water in the condensing jacket was maintained at a temperature of from 2 to 4 C., and the distillate collected in a suction flask, properly connected. After having distilled over about 500 c.c., the distillate was shaken in a

separatory funnel with three successive portions of redistilled ether. The ether solution was dried with three successive portions of pure, fused calcium chlorid. The ether solution was then placed in a distillation flask and most of the ether removed in vacuo at 0 C. (The air for the capillary tube was dried with soda-lime and sulphuric acid.) When the ether was evaporated to about 10 c.c., the solution was quickly transferred to a weighed "half-beaker," the flask having been washed with a small amount of absolute ether. The beaker was placed on an electric hot-plate and the ether thus quickly removed. The contents were weighed. No greater degree of accuracy than 100 per cent. was aimed at. The amount of volatile matter (other than alcohol and water) found was 0.004 per cent. Blanks were run to insure against residues possibly caused by ether or calcium chlorid.

The volatile matter thus secured did not respond to tests for alkaloids with Wagner's reagent or Mayer's reagent. The extract of carduus with 20 per cent. alcohol, treated in exactly the same manner, gave a substance which resembled that from Wine of Cardui in odor, taste and color. With 20 per cent. alcoholic extract of *Viburnum prunifolium* (5 gm. of drug to 100 c.c.) the valerian-like odor predominated. When the original contents were acidified with sulphuric acid and steam passed through, there seemed to be a steady decomposition product (probably vegetable acids) which was carried over. This was true of Wine of Cardui, extract of carduus and extract of viburnum.

The foregoing method was sent to Prof. Edward Kremers of the University of Wisconsin, for criticism. Professor Kremers replied, in part:

> "Your letter dated October 18 was duly received and submitted to Professor Miller. I did not, however, find an opportunity to discuss the subject with him until yesterday morning. . . . . While fully appreciating the fact that practically every method for the determination of volatile constituents in minute quantities is subject to criticism, we are of the opinion that you have done the best that is possible under the circumstances. If you think that it is necessary for your case to have this work duplicated by some one else, Professor Miller is willing to undertake the task."

Subsequently Prof. Emerson R. Miller, also of the University of Wisconsin, undertook an examination of the vola-

tile matter in Wine of Cardui. In his report[20] he gives the volatile matter (by steam) as 0.002 per cent., which agrees with the author's findings.

Another point which excludes the presence of appreciable amounts of volatile oil is that no oily surface or suspension appears in the distillate of Wine of Cardui.

From a therapeutic standpoint, the following sworn testimony of Prof. Torald Sollmann is of interest:

Q.—Doctor, do you know the ordinary dose of volatile oils? *A.*—Three drops.

Q.—Assume that Wine of Cardui contains 0.004 per cent. of volatile principles, other than alcohol and water; can you tell the jury how much Wine of Cardui would have to be used in order to obtain the average dose, namely, 3 drops of the volatile oils? *A.*—One and a quarter gallons.

Q.—What fraction of 3 drops of volatile oil would be in a tablespoonful of Wine of Cardui? *A.*—One three-hundredths of 3 drops.

Q.—What amount, Doctor? *A.*—One three-hundredths of 3 drops.

Q.—Of 3 drops? *A.*—Approximately.

Q.—Have you an opinion as to whether the volatile oil would be of any importance when Wine of Cardui is taken in tablespoonful doses, three or four times a day? *A.*—Such a dose as you named to be present there would have absolutely no significance whatever.

VALERATE DETERMINATIONS

If the supposed virtues of *Viburnum prunifolium* are extracted with 20 per cent. alcohol, they should reside either in the resins or in the valerate compound. Furthermore, a determination of these two factors would be added confirmatory evidence of the quantity of *Viburnum prunifolium* in Wine of Cardui. Warren[21] found the amount of acid precipitable substances in Wine of Cardui to be 0.066 per cent. As a corollary, it was decided to determine the comparative amounts of valerate radical in Wine of Cardui and in the drug *Viburnum prunifolium*.

There are few methods described in the literature for the estimation of the valeric acids. A. C. Chapman[22] described the separation and estimation of isovalerianic acid and acetic acid by treating their sodium salts with 99.5 per cent. acetone. The sodium isovalerate dissolved, while the acetate did not. He obtained satisfactory results. A modification of this method was therefore worked out as being the one best fitted

20. See p. 90.
21. See page 55.
22. Chapman, Alfred C.: The Analyst, 1898, **24**, 114.

to compare the yield of valerianic acid from *Viburnum prunifolium* and Wine of Cardui.

The solution was acidified with 5 gm. of tartaric acid and distilled with steam into a suction flask containing a solution of 4 gm. of sodium carbonate. The suction flask was also connected with a Geissler drying tube, containing some of the sodium carbonate solution, so that air exiting from the apparatus would pass through the sodium carbonate solution, and retain any valeric acid. The entire distillate was evaporated to a small volume in vacuo at 50 C. The very concentrated solution was transferred to a 150 c.c. round bottom flask and evaporated (in vacuo) to almost dryness. The moist precipitate was then broken up and agitated with a glass rod; some purified acetone was added and the whole evaporated (in vacuo) to complete dryness. The flask was removed, 60 c.c. of exactly 99.5 per cent. acetone[23] added, and then placed under a reflux, boiling for three hours. The acetone solution, containing sodium isovalerate was decanted off through a filter and the residue washed with four 10 c.c. portions of 99.5 per cent. acetone. The filtrate was evaporated in a weighed platinum dish, sulphuric acid added, and ignited. The amount of sodium sulphate present, minus the correction factor 0.0014, was then calculated in terms of valeric acid.

Ten gm. of *Viburnum prunifolium* (bark of stem, No. 40 powder) was allowed to macerate twelve hours, with 250 c.c. of 20 per cent. alcohol solution. It was subsequently extracted with two 125 c.c. portions. The percolate was then treated according to the method described above. Quantitative data showed that 10 gm. of *Viburnum prunifolium* yielded an equivalent of 0.0431 gm. of isovaleric acid.

The contents of two bottles of Wine of Cardui were subjected to the valerate determination. Quantitative data showed that two bottles (532 c.c.) yielded an equivalent of 0.0181 gm. of isovaleric acid.

Check determinations and tests of the method were worked out with fluidextract of valerian, Mulford. An extract of *Carduus benedictus* (Formula C) gave no valerate, as was to be expected.

From the foregoing, based on the valerate content, the amount of *Viburnum prunifolium* to each fluidounce of Wine

23. Merck's acetone (highest purity) after being dried over fused $CaCl_2$, was twice redistilled, a Glinsky's fractional distillation tube being used. Only the middle third portion was used. This was then diluted with water to 99.5 per cent. acetone.

of Cardui is equivalent to approximately 4 grains (Formula A uses 6.3 grains) or 2 grains per dose. The U. S. P. dose of *Viburnum prunifolium* is 30 grains.

The amount of valeric acid, contained in a therapeutic dose of fluidextract of viburnum, from these experiments would be 0.0086 gm. The amount of valeric acid in 1 tablespoonful of Wine of Cardui is equivalent to 0.0005 gm. *Deducting, it would take seventeen doses—nearly one bottle—of Wine of Cardui to obtain a therapeutic dose of Viburnum prunifolium.* Based on Warren's resin determination (granting that all of the traces of resin in Wine of Cardui are from *Viburnum prunifolium*), it would require at least seventy-nine doses of Wine of Cardui to obtain the same amount of viburnum resin as in one dose of the fluidextract of *Viburnum prunifolium.*

It can be seen from the valerate experiments, together with Warren's determinations, that Wine of Cardui contains only a very small amount of Viburnum prunifolium extracts.

III

CONCLUSION

Wine of Cardui is a hydro-alcoholic solution, containing no potent drugs, other than 20 per cent. of alcohol. It is the percolate (20 per cent. alcohol being used) from approximately 13 per cent. of *Carduus benedictus* (whole) and 1.4 per cent. of *Viburnum prunifolium*, which percolate has been treated with 0.24 per cent. of anhydrous sodium carbonate, 0.2 per cent. of caramel, and the mixture filtered. Even if *Carduus benedictus* and *Virburnum prunifolium* have therapeutic value, the virtues cannot be extracted with 20 per cent. alcohol, while the volatile oil and valerate are in such small proportions as to have negligible therapeutic effects. This analysis essentially confirms the reports (previously) published in *The Journal of the American Medical Association*, April 11, 1914, and July 18, 1914.

REPORT ON THE ANALYSIS OF WINE OF CARDUI

BY

W. S. Hilpert, Ph.D.

Identification of Specimens.—The bottles used were taken from a box of twelve bottles brought into the Association laboratory by Dr. A. J. Cramp. The case was marked as

follows: "Serial No. A-171; Food and Drugs Act, June 30, 1906, Chattanooga Medicine Co., Chattanooga, Tenn. Notify if not delivered."

Dr Cramp stamped each carton, and as the packages were opened, each bottle with the number "11781" and date of "Oct. 30, 1915." In addition I personally placed my initials "W. S. H." with pen and ink on each bottle label.

Preparation of Material for Examination.—Four bottles of the twelve which I marked A, B, C, and D, respectively, were thoroughly shaken to get all sediment in suspension, and the contents of the four bottles then mixed in a large carefully cleaned and dried bottle. Bottle A bore the number 12 blown in the bottom; bottle B bore the number 10, bottle C the number 11, and bottle D the number 10.

General Physical Properties of the Material.—As received, the bottles of Wine of Cardui all contained a sediment of dark brown matter. The supernatant liquid was also of a dark brown color. The odor resembled valerian. The taste was bitter.

Report of Analysis.—The following determinations were made on Wine of Cardui: alcohol content; specific gravity; solids; ash; alkalinity of ash; absence of heavy metals; suspended matter; total nitrogen; absence of alkaloids; absence of iodids; absence of bromids; absence of emodin-bearing drugs; absence of potassium bitartrate; presence of traces of iron; presence of traces of potassium and sodium; absence of tannin; presence of reducing substances; the amount of matter precipitated by acids.

Alcohol.—Alcohol was determined by the provisional method of the Association of Official Agricultural Chemists.[24] The specific gravity of the distillate (100 c.c. Wine of Cardui diluted and distilled to 100 c.c.) was 0.9768 at $\frac{15.6\ C.}{15.6\ C.}$, corresponding to 19.28 per cent. of alcohol, absolute, by volume.

Specific Gravity.—At $\frac{15.6\ C.}{15.6\ C.}$, 25 c.c. of Wine of Cardui weighed 24.7840 gm., while the same bottle at the same temperature holds 25.0114 gm. of water. This corresponds to a specific gravity of 0.9909.

Solids.—Twenty-five c.c. portions of Wine of Cardui were delivered to weighed dishes, evaporated to dryness and the residues placed in the oven at 100 C. for one hour periods, and weighed after each period. After several weighings it

24. Bull. 107, Bureau of Chemistry, p. 83.

was evident that a continual loss would result; so the drying was stopped after nine hours, when the decrease compared with the previous weight was only from 0.3 to 0.4 mg. One dish contained a residue of 0.7199 gm., corresponding to 2.879 gm. per hundred c.c.; the other dish contained 0.7214 gm. of residue, corresponding to 2.885 gm. per hundred c.c.; average, 2.882 gm. per hundred c.c.

Ash.—The material from the determination of solids was washed into porcelain crucibles, the solution evaporated to dryness and the residue ignited. The char was leached out with hot water and the solution filtered. The filter was washed, dried and burned. The filtrate was added to the ash of the filter, the liquid evaporated and the residue ignited. The first residue weighed 0.1798 gm., corresponding to 0.72 gm. per hundred c.c.; the second residue weighed 0.1619 gm., corresponding to 0.64 gm. per hundred c.c.; average, 0.68 gm. per hundred c.c.

Alkalinity of Ash.—The dishes containing the ashes were covered with watch glasses and an excess of tenth-normal acid run in. After the reaction had ceased, the sides of the dishes and the covers were washed down and the liquid titrated, methyl orange being used as indicator. An excess of tenth-normal alkali was run in and the end-point obtained by running in tenth-normal acid. The first ash required 23.75 c.c. of tenth-normal alkali, corresponding to 9.5 c.c. of normal acid per hundred c.c. of original material. The second ash required 23.27 c.c. of tenth-normal acid, corresponding to 9.3 c.c. normal acid, or an average of 9.4 c.c. normal acid per hundred c.c. of Wine of Cardui.

Absence of Heavy Metals.—About 25 c.c. of Wine of Cardui were made slightly alkaline and evaporated to dryness. The residue was lightly charred and the char leached with acidified water. The liquid was then saturated with hydrogen sulphid. No evidence of any precipitate or darkening could be detected. This showed the absence of such metals as arsenic, antimony, tin, lead, bismuth, cadmium or copper. To test for mercury some of the Wine of Cardui was acidified, filtered, the alcohol evaporated, and the solution saturated with hydrogen sulphid. No trace of precipitate could be found, showing the absence of mercury. In a separate portion which was evaporated, charred and leached as described above, tests were made for the metals, such as iron and calcium. These tests resulted in the detection of traces of iron, aluminum, calcium, magnesium, sodium and potassium.

Suspended Matter.—One hundred c.c. of Wine of Cardui (taken after thoroughly mixing) were filtered through a weighed Gooch crucible, the residue washed with 10 c.c. of water, dried at 100 C., and weighed. One determination yielded 0.0155 gm. of residue and the other yielded 0.0152 gm. of residue; average, 0.0153 gm. per hundred c.c. of Wine of Cardui.

Suspended Matter Insoluble in Ammonia.—The dried crucibles from the preceding determinations were immersed in a little 10 per cent. ammonia water and allowed to stand over night. The next day the filters were sucked dry, washed with 10 c.c. of water, dried at 100 C., and weighed. One crucible contained 0.0009 gm. of residue, and the other 0.0011 gm.; average, 0.0010 gm. per hundred c.c. of matter insoluble in ammonia water.

Nitrogen.—The total nitrogen was determined by the modified Gunning method[25] to include nitrates. Twenty-five c.c. of Wine of Cardui required 79.65 c.c. of tenth-normal acid to neutralize the ammonia distilled over, corresponding to 0.01151 gm. of nitrogen, or 0.046 gm. of nitrogen per hundred c.c.

Absence of Alkaloids.—One hundred c.c. of Wine of Cardui were made slightly alkaline with ammonia water, and the alcohol removed by evaporation. The dealcoholized solution, after being made decidedly alkaline with ammonia water, was shaken out with four portions of 50 c.c. each of ether. The solution was then further extracted with two portions of 50 c.c. each of chloroform, to take out strychnin, should it be present; then with two portions of hot amylic alcohol, 50 c.c. to each extraction, to take out any possible morphin. The combined solvents were evaporated, the residue taken up in acidulated water, the solution filtered, and an excess of iodin solution added. The resulting precipitate was allowed to stand over night, then collected on a filter washed with iodin solution, and finally decomposed with sodium sulphite solution on the filter. The solution was received in a separator, made alkaline and shaken out with chloroform and then with hot amylic alcohol. The solvents were removed by evaporation and the residue taken up with acid water. Ten c.c. of the solution were filtered and the filtrates tested with several alkaloidal reagents. Turbidities were observed, though small, with iodin, mercuric potassium

25. Bull. 107, Bureau of Chemistry, p. 8.

iodid, phosphomolybdic acid and tannin. The entire procedure was repeated until the second precipitate with iodin was obtained. This was again collected and again washed with iodin solution and decomposed with sulphite solution, and the resulting solution made alkaline and shaken out with chloroform and amylic alcohol. The solvents were evaporated, the residue taken up in weak acid solution, the solution filtered and the alkaloidal tests again applied. This time iodin alone gave a faint turbidity, none of the other reagents yielding any signs of the presence of alkaloids. The fact that the usual alkaloidal reagents failed to show the presence of alkaloid in the extract is proof that Wine of Cardui contains no alkaloids.

Iodid and Bromid.—Twenty-five c.c. of Wine of Cardui were made alkaline with a large excess of sodium hydroxid, the solution evaporated to dryness, the residue fused, and the residue leached out with hot water. The solution was filtered and tested for iodid by the addition of ferric chlorid solution and shaking out with chloroform. No violet color appeared in the chloroform, indicating absence of iodid. To make certain that no iodid had been present and converted to iodate, some of the solution was treated with iodid and slightly acidified, but even then no iodin could be detected. Bromin was tested for by adding chlorin water drop by drop to the slightly acidulated solution and shaking with carbon disulphid after each addition. No color of bromin was observed. To determine whether bromate had been formed, some sodium bromid was added to the acid solution, but again no bromin appeared. These tests proved the absence of iodids or bromids, in Wine of Cardui.

Absence of Emodin-Bearing Drugs.—Borntraeger's test[26] was used. Twenty-five c.c. of dealcoholized Wine of Cardui were slightly acidified and shaken with benzene (benzol, C_6H_6). The benzene was separated, washed with water and then shaken with diluted ammonia water. No pink color appeared in the aqueous layer, thus showing absence of emodin-bearing drugs. This test shows the absence of such drugs as aloes, buckthorn, cascara, rhubarb and senna, as well as phenolphthalein.

Absence of Potassium Bitartrate.—As Wine of Cardui has a neutral reaction, no appreciable amount of potassium bitartrate would be expected to be present. However, tests were

26. Borntraeger: Ztschr. f. anal. Chem., 1880, **19**, 165.

made as follows: One hundred c.c. of dealcoholized Wine of Cardui were treated with an excess of basic lead acetate solution, and the resulting precipitate filtered and washed. The precipitate was suspended in water, the liquid saturated with hydrogen sulphid, the lead sulphid removed by filtration, and the filtrate evaporated nearly to dryness. Portions of the solution were tested as follows: A drop of ferrous sulphate was added to some of the solution, a few drops of hydrogen peroxid added, and then an excess of sodium hydroxid solution. No violet coloration appeared, indicating absence of tartaric acid.

A concentrated solution of potassium acetate added to the solution failed to give a precipitate of potassium bitartrate.

Treated with enough calcium hydroxid to neutralize, filtering and allowing to stand over night showed no precipitate, thus showing the absence of tartaric acid.

Absence of Succinates and Benzoates.—The solution which was tested for tartrates was made slightly alkaline with ammonia water, the excess evaporated off and then treated with neutral ferric chlorid. No precipitate resulted. This shows absence of succinates or benzoates.

Absence of Glycerin.—The method used for detecting glycerin was the provisional method described in Bulletin 107, Bureau of Chemistry, p. 83. No glycerin could be detected. This fact, together with the absence of tartrates and succinates, is practically a proof that Wine of Cardui is not prepared from real wine.

Tannin.—Tannin was tested for in dealcoholized Wine of Cardui by the addition of ferric chlorid solution. This showed a slight darkening of the solution, but not enough to show any precipitate. A gelatin solution added to the dealcoholized Wine of Cardui failed to show any precipitate.

Reducing Substances.—Dealcoholized Wine of Cardui was heated with Fehling's solution. A precipitate of cuprous oxid resulted, showing the presence of reducing substances in small amounts. The nature of the reducing substance was not determined.

SUMMARY

From the foregoing I conclude that Wine of Cardui is an aqueous-alcoholic preparation containing 19.28 per cent. of alcohol by volume, and that the preparation is free from potent drugs, other than alcohol. To confirm this conclusion, five doses of Wine of Cardui were swallowed at one time.

The symptoms produced were a burning sensation in the mouth and throat and later in the region of the stomach; still later the cheeks became flushed. No nausea was noticed. As a comparison, the same amount of 20 per cent. alcohol was taken on another day under the same conditions and exactly the same symptoms were experienced. These tests confirm the foregoing conclusions and demonstrate, so far as could be noted in a general way, that whatever effect is noticed from administration of Wine of Cardui can be duplicated by taking an equivalent amount of 20 per cent. alcohol.

REPORT ON THE ANALYSIS OF WINE OF CARDUI

BY

A. H. Clark, B.S.

PROFESSOR OF CHEMISTRY, UNIVERSITY OF ILLINOIS SCHOOL OF PHARMACY

I submit the following report on the chemical examination of Wine of Cardui.

The material used was purchased from Peter Van Schaack and Sons, Oct. 28, 1915. Each bottle was received in an unopened package. The contents of nine bottles were combined, and the entire examination is of this sample. Three bottles of this purchase are still in my possession, unopened and sealed by me.

Details of the methods are not given, but will be supplied at any time if desired.

I found Wine of Cardui to be a dark, reddish brown liquid, turbid, depositing some matter on standing. It has a peculiar valerian-like odor, a burning, very bitter, but not entirely unpleasant taste, and is faintly alkaline, almost neutral.

Examination for Volatile Potent Drugs.—This examination was conducted after the plan of Autenrieth (Warren) 1915 edition. It included the following:

Phosphorus and its compounds.

Hydrocyanic acid and its compounds.

Carbolic acid, chloroform, chloral hydrate, nitrobenzene, anilin, ethyl alcohol, acetone, benzaldehyd.

Only ethyl alcohol was found.

Nonvolatile Potent Drugs.—The ether extract from the acid solution was considerable. It was yellowish, opaque and

very bitter. It was soluble in water and alcohol, and had a marked acid reaction. It did not contain nitrogen, and did not respond to any of the alkaloidal reactions save iodin. It reduced Fehling's solution, but gave an amorphous reddish precipitate, changing the blue color of the solution to a dirty green. Nothing crystalline could be obtained from this residue.

This would exclude picrotoxin, colchicin, picric acid, caffein, acetanilid, phenacetin, antipyrin and veronal.

Alkaloids.—Extracting the alkaline solution with ether gave very little residue, and this residue did not give alkaloidal precipitates with any of the following reagents: Mayer's solution, bismuth-potassium iodid, phosphomolybdic acid, mercuric chlorid, gold chlorid, platinic chlorid, tannic acid. A slight reaction was given with iodin. This would exclude all alkaloid-bearing drugs.

Metallic Salts.—The Fresenius-von Babo method was used. No metals of any kind could be found save a trace of iron, some calcium, sodium and potassium. Possibly traces of magnesium.

Nitrogen was determined by the Kjeldahl-Gunning method modified to include the nitrogen of nitrates and also unmodified for nitrates.

Nitrogen in the ash was determined by reduction with zinc and iron in alkaline solution.

Reducing sugars were determined by the Allihn method.

Potassium was determined as potassium platinic chlorid.

Quantitative determinations for calcium and sodium were not complete.

The following quantitative values were found:

Specific gravity (at 15.6 C.)	0.9919	0.9918
Alcohol (by volume at 15.6 C.)	19.55 per cent.	
Solids (gm. in 100 c.c.)	2.92	2.84
Ash (gm. in 100 c.c.)	0.9484	0.9444
Ash insoluble in water (gm. in 100 c.c.)	0.1104	0.1164
Ash insoluble in acid (gm. in 100 c.c.)	0.00028	
Total nitrogen, unmodified (gm. in 100 c.c.)	0.126	0.124
Total nitrogen, modified (gm. in 100 c.c.)	0.123	0.123
Nitrogen in the ash (by reduction with zinc and iron in alkaline solution) gm. in 100 c.c.	0.028	
Alkalinity of soluble ash (c.c. of normal sodium hydroxid per hundred c.c. of original material)	8.58	8.58
Alkalinity of insoluble ash (c.c. of normal sodium hydroxid per hundred c.c. of original material)	1.92	
Alkalinity of total ash (c.c. of normal sodium hydroxid per hundred c.c. of original material)	10.50	

Insoluble residue (gm. in 100 c.c.)	0.0134	
Reducing sugars, before inversion (gm. in 100 c.c.)	0.5776	0.5660
Reducing sugars, after inversion (gm. in 100 c.c.)	0.6552	0.6522
Reducing sugars, after complete hydrolysis (gm. in 100 c.c.)	0.6868	0.6744
Potassium (gm. in 100 c.c.)	0.2711	0.2714
Resin-like substances (gm. per hundred c.c.) about	0.040	
Alkaloids	absent	
Iodids and bromids	absent	
Emodin-bearing drugs	absent	
Caramel	present	
Tannin	present in very small amounts	

CONCLUSION

This analysis shows conclusively that Wine of Cardui contains none of those drugs except alcohol which are considered active, or potent.

A preparation containing *Carduus benedictus, Viburnum prunifolium,* sodium carbonate and caramel in 20 per cent. alcohol was prepared according to "Formula A" submitted by Dr. Leech of the Chemical Laboratory of the American Medical Association, and from drugs handed to me by him.

This preparation corresponds closely in physical properties with Wine of Cardui. Its color, odor, taste, etc., were very much like Wine of Cardui. The specific gravity of this preparation was 0.9937; the total solids 3.2 gm. per 100 c.c.; and total ash 1.116 gm. in 100 c.c. The same bitter principle was present. From this I conclude that Wine of Cardui must have essentially the same composition as this preparation.

To confirm the conclusions drawn from the chemical analysis I took four tablespoonfuls of Wine of Cardui, about an hour before lunch one day. The only effect produced was a warming sensation in the stomach, a flushing of the face, and a slight glowing sensation of the skin. The following day, at about the same hour, I took the same quantity of 20 per cent. alcohol. The sensations experienced were about the same as those with Wine of Cardui.

I also removed the alcohol from an entire bottle of Wine of Cardui and drank all the liquid residue at once. No noticeable effect was produced. This certainly confirms the conclusions of the analysis, namely, that none of those drugs which are considered active or potent, are present.

I also exaporated the alcohol from 5 ounces of the "synthetic" preparation and took the entire quantity of the liquid residue at once. No noticeable effect was produced.

REPORT ON THE ANALYSES OF WINE OF CARDUI

BY

W. D. McAbee

Assistant Chemist, Indiana State Board of Health

The qualitative examination was made of samples of Wine of Cardui that were purchased from the larger druggists of this city [Indianapolis] who do not allow their stock to become aged, while the quantitative results were obtained from a set of samples collected from druggists in the smaller towns who sometimes keep their stock for several years.

In the tabulation of results the bottles are numbered in the order of their supposed age, No. 1 being the oldest.

Appearance: Clear liquid. Color of "black coffee."

Taste: Insipid. Slightly bitter.

Odor: Slightly valerian-like except in Nos. 1 and 2.

Solids: Brownish, resinous mass with slightly bitter taste.

Ash: Typical vegetable ash containing sodium, potassium and calcium salts.

Sample evaporated one-half and made up to original volume with water. No sediment or separation.

Dealcoholized sample made acid and extracted.

Petroleum Ether: Brownish, resinous mass with slightly bitter taste.

Ether: Yellow mass; no taste.

Chloroform: Very slightly gray; no taste.

None of these extracts gave reactions for alkaloids, and no emodin could be detected. They could not be identified by any test given in Fuller, "The Qualitative Analysis of Medicinal Preparations."

Dealcoholized sample made alkaline and extracted. Results same as acid extraction. Therefore, no potent alkaloids were present.

Sample distilled. Distillate slightly turbid, evidently from small amount of volatile oil. Distinct odor of valerian. Bromin, iodin and arsenic were absent.

Wine of Cardui, therefore, is apparently an aqueous-alcoholic solution of the extracts of some drug containing a bitter principle and another bearing valerianic acid, such as valerian itself, or black haw, etc.

The analyses indicate that, aside from the alcohol, Wine of Cardui contains no potent ingredient in quantities capable of producing any physiologic effects.

No. of Sample*	1	2	3	4	5	6
Specific gravity	0.9938	0.9924	0.9976	0.9865	0.9867	0.9883
Solids (gm. per 100 c.c.)	3.825	3.534	3.434	2.605	3.190	2.936
Alcohol (by volume)	19.07	19.44	14.77	21.00	21.90	19.57
Ash (gm. per 100 c.c.)	1.066	0.974	1.004	0.719	0.795	0.912
Lead number	2.084	2.080	2.692	1.600	1.496	1.456
Ether extract (gm. per 100 c.c.)	0.0380	0.0299	0.0202	0.0288	0.0318	0.0299
Alkalinity of ash (c.c. N/1 NaOH per 100 c.c. of material)	.....	.....	.....	.....	9.3	9.9
Tannin	.....	.....	.....	.....	+	+
Reducing substances (usually calculated as glucose) (gm. per 100 c.c.)	.....	.....	.....	.....	0.46	0.49
Volume of container, c.c.	300	300	300	275	290	275

* Samples are numbered according to supposed age.

REPORT ON THE ANALYSES OF WINE OF CARDUI AND ITS SYNTHETIC IMITATIONS

BY

Alviso Burdett Stevens, Ph.C., Ph.D.

PROFESSOR OF PHARMACY AND SECRETARY OF THE COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

I have worked on three samples of Wine of Cardui, two of which were unopened, original packages furnished by the Laboratory of the American Medical Association. Each of them was marked with the name "L. E. Warren" written in ink. The other specimen I obtained in the open market. I found but little variation in these samples, which is apparent only in the percentage of alcohol and in the specific gravity. The ash was slightly alkaline, and contained small quantities

of carbonate and chlorids. The preparation does not contain any bromids, iodids, alkaloids, tannins, emodin-bearing drugs or metallic poisons. In fact, the small amount of ash would exclude all medicinally active inorganic salts, except the more potent ones, like arsenic and mercury, which are not present. The preparation contains small quantities of nitrogen, but the quantity was not determined. It contains a small quantity of a bitter principle, the character of which I have been unable to determine positively and possibly a trace of resin. I have compared it with the bitter principle obtained from each of several drugs, but without finding any which it closely resembles. Tartaric acid was not present in Wine of Cardui, which would have been the case had any of the natural wines been used in its manufacture. From the examination I feel certain that Wine of Cardui does not contain any medicinally active substances except alcohol, with possibly some slight tonic effect from the bitter principle.

The quantitative findings are given herewith:

Specific gravity	0.9903	0.9895	0.9902
Alcohol (by volume).....	19.3	19.6	20.4
Solids (gm. in 100 c.c.)....	2.83	2.80	
Ash (gm. in 100 c.c.).....	0.88	0.85	

In order to ascertain if Wine of Cardui contained any decidedly active drug a few physiological tests were made. I began by taking the dose recommended, and then increased until 2 ounces were taken at a single dose. This produced a slight, but decided dizziness, evidently due to the alcohol. For comparison an equal quantity of alcohol (2 ounces of 20 per cent. alcohol) was taken on another day. The effect was the same as that produced by the Wine of Cardui. Later I took, at one dose, the contents of one bottle, after having removed the alcohol from two thirds of the preparation by evaporation at a temperature below 40 C. The only noticeable affect was that due to the alcohol.

Wine of Cardui was evaporated to dryness and the residue treated with various solvents. The several extracts thus obtained were chemically compared with similar extracts from various drugs. The only extracts giving identical results were those obtained from a mixture of *Carduus benedictus* and *Viburnum prunifolium*.

Feb. 29, 1916, I made a Compound Tincture of Cardui similar to "Wine of Cardui" as follows:

Carduus benedictus, whole	142.6	Gm.
Viburnum prunifolium	15.75	Gm.
Alcohol	241.8	Cc.
Water sufficient to make	1135.5	Cc.

This was prepared by maceration and decantation. To this extract there were added 2.7 gm. of anhydrous sodium carbonate and 2.3 gm. of caramel.

The odor, taste and physical appearance of this synthetic preparation were identical with Wine of Cardui. When compared chemically the two preparations were identical. Quantitative determinations gave practically the same results, as seen from the following table:

	Wine of Cardui	Synthetic Preparation
Specific gravity	0.9903	0.9916
Nonvolatile solids (gm. per 100 c.c.)	2.83	2.962
Apothem (extractive)	0.58	0.57
Ash	0.88	1.16

The slightly higher results obtained from the synthetic preparation may be due to more perfect exhaustion, or, to a slight variation in the quality of the drugs used. I found that the larger the proportion of the stems of *Carduus benedictus* to leaves, the less the yield of ash and extractive.

A bottle of Wine of Cardui was evaporated to dryness at about 60 C. and the residue divided into two equal parts. One part was made into sixteen pills. To the remaining part 0.5 gm. of magnesium oxid was added and the mass made into nine compressed tablets. Another half bottle was evaporated and the residue put into eight capsules. A half of a bottle of Wine of Cardui was mixed, in an evaporating dish, with 27 c.c. of glycerin and kept at about 45 C. until the alcohol was all removed. The solution was then diluted to its original volume, by the addition of water and glycerin, in such proportion that the finished preparation contained 40 per cent. of glycerin. This solution was kept for several days,. at a temperature of from 24 to 38 C., without apparent change.

Duplicates of all of the above preparations were prepared from the Synthetic Wine of Cardui. All of above preparations were preserved for presentation to the Court.

CONCLUSIONS

1. Wine of Cardui does not contain any potent ingredient except alcohol.

2. Wine of Cardui is not a wine, except in name.

3. Wine of Cardui probably contains extracts from *Viburnum prunifolium* and *Carduus benedictus.*

4. Alcohol is not necessary as a preservative of the constituents of Wine of Cardui.

5. The presence of 20 per cent. of alcohol in Wine of Cardui, without medicinally active constituents, permits its use as an alcoholic beverage.

REPORT ON THE ANALYSIS OF WINE OF CARDUI

BY

Ralph W. Webster, M.D., Ph.D.

Assistant Professor of Pharmacologic Therapeutics, Rush Medical College

The specimen of McElree's Wine of Cardui, received from the Laboratory of the American Medical Association, Feb. 3, 1915, and the specimens received from the same source later were submitted to examination with the following results:

Appearance: A dark brown liquid of neutral reaction, a bitter taste and a valerian-like odor.

Specific gravity (at 15.6 C.; pycnometer method)	0.9936	
Alcohol* (specific gravity of distillate)	0.9759	
Alcohol (by weight)	16.54	per cent.
Alcohol (by volume)	20.33	per cent.
Alcohol (gm. per hundred c.c.)	16.13	
Solids (gm. per hundred c.c.)	3.52	
Volatile matter (gm. per hundred c.c.)	96.48	
Ash (gm. per hundred c.c.)	0.763	
Insoluble residue (gm. per hundred c.c.)	0.041	
Total nitrogen (gm. per hundred c.c.)	0.048	
Alkalinity of ash (c.c. of normal sodium hydroxid per hundred c.c. of original material)	11.41	
Alkaloids	negative	
Reducing substances	positive	
Iodids and bromids	negative	
Emodin-bearing drugs	negative	
Heavy metals (except faint trace of iron)	negative	
Cnicin.....a very little crystalline residue obtained from 1 entire bottle.		

* By use of Hehner's tables.

The analysis as reported above, shows that McElree's Wine of Cardui is a water-soluble (20 per cent. alcohol) solution of certain drug extractives containing aside from the alcohol, no potent drugs of any type in appreciable quantities.

In order to verify this chemical examination by actual administration of Wine of Cardui and observation of its effects, I, personally, took, at two successive intervals in a period of a half day, an entire bottle of Wine of Cardui; one-half bottle at each dose. The effects, observed after taking

the entire bottle, were controlled by taking exactly the same amount of alcohol in water on a different day. The effects observed on myself were identical after taking the Wine of Cardui and the alcohol; viz., absolutely no effects other than those of alcohol. There was no emetic effect, no cathartic effect and no visible effects other than those attributable to the alcohol ingested.

To rule out the effect of alcohol in Wine of Cardui, I evaporated the alcohol from an entire bottle of Wine of Cardui, dissolved the residue in about 8 ounces of water, divided this aqueous solution into two equal portions and took one half in the morning and the other in the afternoon of the same day. This dealcoholized mixture produced absolutely no results beyond those attributable to the bitter taste. There was no sensation of nausea, no emesis, catharsis nor any other action observed as a result of taking the dealcoholized residue of an entire bottle of Wine of Cardui.

REPORT OF THE ANALYSIS OF WINE OF CARDUI

BY

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On Thursday, Jan. 28, 1915, I received a package from the American Medical Association sealed by L. E. Warren on Jan. 26, 1915, containing three unbroken cartons of Wine of Cardui. All bore the signature "L. E. Warren" on the outside label. Two were further labeled "High-King" and the third was marked "Stevenson."

One of the cartons marked "L. E. Warren, 1-26-15 High-King" was subjected to analysis. Various other cartons of Wine of Cardui were purchased in drug stores in Madison, Wis. In all cases the package was carefully inspected to determine that it was sealed and was intact as when it left the manufacturer.

CHEMICAL ANALYSIS

The liquid was of a dark brown or mahogany color, murky from suspended material, and had a disagreeable valerian-like odor. Its reaction towards litmus was neutral. Quali-

tative tests failed to reveal the presence of *any therapeutically active* or useful drugs except alcohol and a substance, not an alkaloid, which had a bitter taste but otherwise was inert. The following quantitative results were obtained.

QUANTITATIVE ANALYSIS

Specific gravity at 21 C	0.9900
Alcohol (by weight)	16.2 per cent.
Alcohol (by volume)	20.25 per cent.
Total solids (gm. per hundred c.c.)	2.90
Ash (gm. per hundred c.c.)	0.81
Total nitrogen (gm. per hundred c.c.)	0.055
Total nitrogen (calculated as potassium nitrate, gm. per hundred c.c.)	0.397
Glucose (all reducing sugars, gm. per hundred c.c.)	0.95
Dextrin (gm. per hundred c.c.)	0.25
Suspended matter acid precipitable substances and undetermined substances (by difference)	0.493

NOTES ON THE ANALYSIS

Nitrogen was determined by the Kjeldahl method, the salicylic acid and zinc modification being employed in order to insure the reduction of nitrates. The nitrate may be tested for directly in the material by use of the diphenylamin reaction. The alcohol-free material was employed and the acid-precipitable substances precipitated with dilute hydrochloric acid. The flocculent precipitate and suspended material were removed by filtration. With this solution it was attempted to make an approximate determination of the nitrate colorimetrically with the diphenylamin reaction and a known strength of potassium nitrate solution for comparison. Both the preparation and the known solution of the nitrate were carefully diluted to the extinction point. By this method the Wine of Cardui was found to contain inorganic nitrates in amount which would correspond to from 0.35 to 0.4 per cent. potassium nitrate, indicating that the very small amount of nitrogen which it contains is practically all in the form of inorganic nitrate. That the diphenylamin reaction is due to nitrate was proved by reducing the nitrate to nitrite, using zinc dust and testing for the nitrite with the Griess reagent or potassium iodid and starch paste in acid solution. This reaction must be performed with material freed from alcohol because the latter decomposes the nitrite as quickly as it is formed.

Glucose.—This determination was made with Fehling's solution and the total reducing material calculated as glucose. That the "wine" contains glucose or fructose is proved by the fact that it yields glucosazone on treatment with phenyl-

hydrazin. Furthermore, after distilling off the alcohol the residue readily ferments when yeast is added and the material placed in the incubator. If the "wine" be precipitated with basic lead acetate and the filtrate examined in the polariscope, it is found to be practically optically inactive, which would indicate that the glucose had been racemized by some treatment.

Dextrin.—After treatment with a little dilute hydrochloric acid, the filtrate from the "wine" on further treatment with four volumes of alcohol yields a small amount of a light colored flocculent precipitate. This was filtered off, washed with absolute alcohol and dried. It was dissolved in water. The solution does not reduce Fehling's solution, but after hydrolysis with acid it does reduce Fehling's solution. The quantitative determination of the dextrin was made by completely hydrolyzing a portion of "wine" and then determining its reducing power with Fehling's solution. The difference between the reducing power before and after hydrolyzing is calculated as due to dextrin.

Suspended Matter, Acid Precipitable Substance and Undetermined Substances.—On filtering or centrifuging a considerable amount of material may be removed. This on microscopic examination proved to be rich in yeast cells and to contain some bacteria. The latter are not very numerous and consist of coccoid and bacillary forms. The latter look like the typical organisms found in most grain.

The acid-precipitable substances were not determined quantitatively, but it was noted that on faintly acidifying the "wine" with dilute acids a dark brown flocculent precipitate is thrown out which, when filtered off, leaves the solution much lighter in color. This was filtered off and thoroughly washed with acidulated water. This material does not reduce Fehling's solution either before or after hydrolysis. The precipitate is amorphous. It is very soluble in dilute alkalies. The suspended matter and acid-precipitable substances undoubtedly account for a considerable part of the "undetermined" portion of 0.493 per cent., and leaves very little material to be accounted for.

Alkaloids.—One hundred c.c. of Wine of Cardui were treated with dilute hydrochloric acid and filtered. The filtrate was exactly neutralized with sodium hydroxid, the material evaporated on the water bath to remove the alcohol, made up to 50 c.c. with water, acidified with sulphuric acid and filtered. The solution was placed in a separator, chloroform

added and the mixture made alkaline with sodium hydroxid. After thorough extraction the chloroform was removed, filtered and evaporated. The residue, which was not large, was a resinous amorphous, fatty waxy mass not soluble in water or dilute acid. It was entirely tasteless (excluding quinin or strychnin). After twenty-four hours' extraction of the residue with dilute sulphuric acid and filtering, the filtrate gave no precipitate with phosphotungstic acid, Bouchardat's reagent or other alkaloidal reagents, indicating complete absence of alkaloids.

THE EFFECT OF WINE OF CARDUI ON MAN

March 13, 1916, at 11:30 a. m., I swallowed the contents of an entire bottle of Wine of Cardui purchased in the open market in Madison the same day and with the seal of the carton unbroken. The effect became apparent in ten minutes, and increased in intensity for one hour to an hour and one-half. There was absolutely no nausea or vomiting at any stage of the action of the material. The symptoms produced were a tingling and numbness of the lower limbs, unsteadiness of gait, difficult articulation, vision somewhat blurred, poor muscular coordination. About 2:30 p. m. the effects began to wear off and a severe headache developed. There was also a marked drowsiness. The headache increased in intensity and I was forced to go to bed for three hours. I awoke feeling better, but slight headache remained until bedtime. The next morning I felt all right again. The results of this experiment are very striking when compared with the strictly negative result produced on the same individual by taking the contents of the entire bottle of Wine of Cardui from which the alcohol had been first removed as recorded in my first report. The conclusion reached is that *Wine of Cardui produces purely an alcoholic effect, the other constituents being entirely inert. It may be readily used as an intoxicant.*

SUMMARY

The Wine of Cardui is approximately a 20 per cent. alcoholic preparation containing about 0.4 per cent. of potassium nitrate, about 1 per cent. of glucose, 0.25 per cent. of dextrin and a small amount of plant extractives. It is free from alkaloids, and the chemical analysis fails to reveal any substance except alcohol in sufficient quantity to be useful in the treatment of any disease or pathologic condition. Furtherfore, as a result

of the analysis of various synthetic preparations (see this report, page 66), I am convinced that Wine of Cardui contains extractives, removed by percolating approximately 13 per cent. (gm. per c.c.) of *Carduus benedictus* and 1.4 per cent. of *Viburnum prunifolium*. Caramel (0.2 per cent.) and anhydrous sodium carbonate (0.24 per cent.) are added, and the liquid filtered. The amounts of extractives removed are very small.

REPORT OF THE ANALYSIS OF WINE OF CARDUI

BY

Emerson R. Miller, Ph.C., B.S., Pharm.M., M.S.

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Specimens of Wine of Cardui were obtained from a wholesale house in Chicago and were subjected to chemical examination. The liquid had a reddish brown color, a slight valerian-like odor and a bitter taste. Its reaction toward litmus was neutral. Qualitative tests were made with the following results:

Tannin: a very small amount.

Iodids: none.

Bromids: none.

Plant bases: (*a*) Some of the liquid was made alkaline with ammonia water and extracted with ether. When tested in the usual manner with alkaloidal reagents, slight indications of the presence of basic substances were obtained. (*b*) One bottle of the preparation was made alkaline with sodium carbonate and then extracted with chloroform. An acidulated aqueous extract prepared from the chloroformic solution gave very noticeable precipitates with several alkaloidal reagents. Considering the fact that a whole bottleful of the preparation was used in this experiment, the basic substance or substances indicated must be present in very small amount.

Quantitative determinations were made with the following results:

Specific gravity at 25 C.	0.9910
Alcohol by volume	22.5 per cent.
Solids (gm. per hundred c.c.)	3.480
Ash (gm. per hundred c.c.)	1.05

Alkalinity of ash (c.c. normal alkali per hundred c.c. of original material)..... 11.36
Sugars (gm. per hundred c.c.):
Reducing power expressed as glucose..... 0.942
Reducing power after inversion..... 1.002
Volatile matter (gm. per hundred c.c.)..... 0.026*
Volatile matter (gm. per hundred c.c.)..... 0.002†

* The preparation was acidulated with sulphuric acid, distilled with steam, the distillate shaken out with ether, the ether solution dehydrated with anhydrous calcium chlorid and the ether then evaporated at low temperature under diminished pressure.

† In this experiment the neutral preparation was distilled with steam and the distillate extracted with petroleum ether (boiling point from 25 to 30 C.). The solvent was evaporated at low temperature and pressure.

In the first distillation experiment the distillate was collected in 50 c.c. fractions. The first five fractions before extraction with ether were examined with a polariscope, with the result that none of them showed any effect on the plane of polarized light.

The index of refraction was determined for the first eight fractions. For the purpose of comparison, a mixture of alcohol and water containing about 23 per cent. by volume of alcohol was distilled with steam, this distillate also being collected in 50 c.c. fractions and the index of refraction for each determined.

The following values were obtained:

	$^{n}D_{14}$ for Fractions from Cardui	$^{n}D_{14}$ for Fractions from 23 Per Cent. Alcohol
Fraction 1.....	1.3649	1.3654
Fraction 2.....	1,3571	1,3470
Fraction 3.....	1.3412	1.3350
Fraction 4.....	1.3349	1.3340
Fraction 5.....	1.3349	1.3339
Fraction 6.....	1.3335	1.3335
Fraction 7.....	1.3335	1.3335
Fraction 8.....	1.3335	1.3335

Such differences as exist between these values for the corresponding fractions are undoubtedly due mainly to difference in the rate of distillation. The rate was not as uniform for the 23 per cent. alcohol as it was for the Cardui, being slower for Fraction 1 than for the same fraction from Cardui, and in the case of Fractions 2 and 3 it was faster than for the corresponding fractions from Cardui.

From the work done I conclude that Wine of Cardui does not contain any physiologically active substances, except alcohol, in more than extremely small amounts, and that the preparation might be used as an alcoholic beverage.

MISCELLANEOUS INVESTIGATIONS RELATING TO THE ANALYSIS OF WINE OF CARDUI

BY

L. E. Warren, Ph.C., B.S.

In addition to the analyses of Wine of Cardui and the analyses of the several trial products prepared while synthesizing that preparation, many experiments were carried out in the laboratory of the American Medical Association and elsewhere in order to obtain further information concerning Wine of Cardui and its supposed ingredients.

Specimens of *Viburnum prunifolium* (root bark and stem bark), of *Viburnum opulus* (U. S. P. VIII), of *Acer spicatum* (an alleged substitute for *Viburnum opulus*) and of *Cnicus benedictus* were obtained from reliable sources. These were authenticated by a pharmacognocist. Fluidextracts were prepared from these drugs by the standard methods, specimens of the preparation were sent to Dr. J. D. Pilcher, a competent pharmacologist, in order that their physiologic effects on the uterus might be determined, and in most cases the finished products were subjected to analysis. So far as practicable, the results were compared with those obtained from the corresponding preparations as put up by a pharmaceutical manufacturer and obtained on the open market. Some of the drugs were subjected to the Stas-Otto method for the analysis of plants and the several fractions obtained sent to a pharmacologist for testing. Numerous experiments on the resins of viburnum were also carried out.

Viburnum Prunifolium

Bark of Root.—A quantity of unground black haw (U. S. P. VIII) was ground in the laboratory of the Association to No. 40 fineness. Ten gm. of the powdered drug were extracted by 94 per cent. alcohol until exhausted, the solvent evaporated and the residue dried in the air and weighed. The residue weighed 2.3354 gm., or 23.35 per cent. The residue was treated by the Stas-Otto method. The water-insoluble portion (resin) weighed 0.8613 gm., equivalent to 8.61 per cent. of the weight of material taken. The ether-soluble portion (from acid solution) weighed 0.0431 gm., equivalent to 0.43 per cent. of the weight of material taken. The ether soluble portion (from alkaline solution) weighed 0.0059 gm., equivalent to 0.059 per cent. of the weight taken.

The residue obtained from the alkaline solution by shaking with ether was taken up in a little warm, acidified water, the solution filtered, and the usual alkaloidal reagents applied to the filtrate. A very faint opalescence was given with mercuric-potassium iodid, and a faint cloudiness with iodin solution. These tests indicate that alkaloids, if present at all in viburnum, must occur in extremely minute amounts. The iodin precipitate was decomposed by a slight excess of sulphurous acid, the solution made alkaline with ammonia water, shaken several times with chloroform, the solvent evaporated, the residue taken up in acidified water, and the solution tested for alkaloids. A negative result was obtained.

Stem Bark.—The work was duplicated so far as concerned the alkaloidal tests on an authenticated specimen of the stem bark of *Viburnum prunifolium.* The results were negative.

These findings are not in accord with the statements of Shennan,[1] who reported the isolation of about 0.5 per cent. of a syrupy alkaloid from the bark of *Viburnum prunifolium.*

Fluidextract.—A fluidextract was prepared from the bark of the root, according to the method described in the U. S. Pharmacopeia VIII; and from the bark of the stem (No. 60 powdered) a fluidextract was prepared according to the method described in the U. S. Pharmacopeia VII (1890). The alcoholic content, the residue on drying and the resin content were determined. A specimen of each fluidextract was sent to Dr. Pilcher for pharmacologic tests. The results are given in the following table:

VIBURNUM PRUNIFOLIUM

Fluid extract Viburnum prunifolium	Solids (gm. per hundred c.c.)	Alcohol (% by volume)	Resins (gm. per hundred c.c.)	Effect on uterus (Pilcher's report)
U. S. P. VIII (Laboratory specimen)	12.25	50.18	2.27	Inert
U. S. P. 1890 (Laboratory specimen)	25.26	52.66	3.98	Inert
U. S. P. VIII (Mulford)	14.04	55 (declared)	2.82	

VIBURNUM OPULUS

A specimen of genuine *Viburnum opulus* bark was received from a drug dealer (Parke, Davis & Co.). After being authenticated by a pharmacognocist, it was ground to a No. 40

1. Shennan: Edinburgh Med. Jour., 1896, **42**, 404.

powder and a fluidextract prepared from it according to the method described in the U. S. P. VIII. The residue on drying and the alcohol content of the fluidextract were determined. A preparation bearing the name of "Fluid Extract of Viburnum Opulus, U. S., P.," was purchased on the open marked and examined as to its residue on drying. It was declared to contain 55 per cent. of alcohol. On dilution with water it gave no valerian-like odor. Several years ago Farwell[2] pointed out that there was no genuine cramp bark on the market, the genuine article having been entirely replaced by the bark of the mountain maple, *Acer spicatum.* For these reasons it was suspected that the fluidextract purchased was spurious. A specimen of the genuine preparation was sent to Dr. J. D. Pilcher, a pharmacologist, in order that it might be tested for its physiologic effects on the uterus.

The findings for the genuine specimen as well as for the specimen thought to be spurious are given in the accompanying table.

VIBURNUM OPULUS

Fluid extract Viburnum opulus	Alcohol (% by volume)	Solids (gm. per hundred c.c.)	Effect on the uterus (Pilcher's report)
Laboratory specimen....	52.68	20.49	Inert
Mulford (believed to be spurious)	55 (declared)	13.35	

ACER SPICATUM

A specimen of mountain maple bark, *Acer spicatum,* was obtained and, after authentication by a pharmacognocist, was ground to a No. 40 powder. A fluidextract was prepared from the powder according to the method described in the U. S. P. VIII for *Viburnum opulus.* The fluidextract was examined for alcohol content and solid residue, and a specimen sent to a pharmacologist in order that its physiologic action on the uterus might be determined. The results are given in the accompanying table. Also are given for comparison the findings for a preparation sold as fluidextract of *Viburnum opulus,* but which appeared to have been prepared from *Acer spicatum.*

2. Farwell:(Bull. Pharm., 1913, **17**, 65.)

ACER SPICATUM

Fluid extract Acer spicatum	Alcohol (% by volume)	Solids (gm. per hundred c.c.)	Effect on the uterus (Pilcher's report)
Laboratory specimen....	58.14	9.87	Inert
Mulford brand. Labeled fl. ext. Vib. opulus....	55 (declared)	13.35	

Cnicus Benedictus

A specimen of blessed thistle herb, *Cnicus benedictus,* was obtained and, after authentication, was ground to No. 40 powder. A fluidextract was prepared from the powdered drug according to the method described in the U. S. P. VIII for eupatorium. The alcoholic content and the solid residue of the laboratory preparation and of a commercial specimen of the fluidextract were determined. A specimen of the preparation (laboratory specimen) was sent to a pharmacologist in order to determine its physiologic effect on the uterus. The results are given in the following table:

CNICUS BENEDICTUS

Fluid extract Cnicus benedictus	Alcohol (% by volume)	Solids (gm. per hundred c.c.)	Effect on the uterus (Pilcher's report)
Laboratory specimen	37.84	21.46	Inert
P. D. & Co. brand.....	40 (declared)	18.84	

Castanea Dentata

During the Wine of Cardui investigations, Dr. J. D. Pilcher and his pupils tested authenticated preparations of a considerable number of drugs for their physiologic effects on the uterus.[3]. The drugs studied were believed to be constituents of nostrums sold as "women's tonics," "female weakness" remedies, "female regulators," etc. These drugs and commercial specimens of fluidextracts bearing the same name were obtained by the laboratory and forwarded to Dr. Pilcher. In some cases the fluidextracts were prepared in the laboratory

3. Pilcher, J. D.; Burman, G. E., and Delzell, W. R.: The Action of the So-Called Female Remedies on the Excised Uterus of the Guinea-Pig, Arch. Int. Med., November, 1916, p. 557.

from authenticated drugs and the finished preparations sent for pharmacologic tests. Among the drugs studied, in addition to those previously mentioned in the analyses of Wine of Cardui, were blue cohosh (*Caulophyllum thalictroides*), figwort (*Scrophularia nodosa* var. Marylandica), helonias (*Chamaelirium luteum*), life root (*Senecio aureus*), motherwort (*Leonurus cardiaca*), pasque flower (*Pulsatilla pratensis*), passion flower (*Passiflora incarnata*), squaw vine (*Mitchella repens*), skull cap (*Scutellaria lateriflora*), unicorn root (*Aletris farinosa*), valerian (*Valeriana officinalis*), Jamaica dogwood, (*Ichthyomethia piscipula*), ladyslipper (*Cypripedium pubescens*), and wild yam (*Dioscorea villosa*). Since these drugs have been reputed by some to possess therapeutic value, it seemed desirable to compare their physiologic action with that of some drug which had never been suggested as a remedy in diseases of women, and which was not supposed to possess therapeutic merit of any kind. Chestnut bark appeared to fulfil such requirements.

Accordingly a specimen of chestnut bark, *Castanea dentata*, was obtained from the living tree growing in northeastern Ohio. The bark was dried somewhat and ground to a No. 40 powder. A fluidextract was prepared from the ground bark according to the method described in the U. S. P. VIII for fluidextract of *Viburnum prunifolium*. The residue on drying and the alcoholic content were determined, and a specimen of the preparation was sent to a pharmacologist in order to determine whether or not it was capable of producing any physiologic effects on the uterus. The findings are given in the accompanying table.

CASTANEA DENTATA

Fluid extract Castanea dentata	Alcohol (% by volume)	Solids (gm. per hundred c.c.)	Effects on the uterus (Pilcher's report)
Laboratory specimen....	53.24	17.48	Practically inert
Commercial specimen....	Could not be obtained, as chestnut bark is not used in medicine.		

METHOD OF OBTAINING THE EXTRACTIVES FROM WINE OF CARDUI FOR PHARMACOLOGIC INVESTIGATIONS

Solution of Suspended Matter.—Two liters of the preparation were filtered through a Gooch crucible, and the residue washed with a few cubic centimeters of water. The washed

residue was then dissolved, so far as possible, in 20 per cent. alcohol containing a little ammonia, and the solution made up to given volume. One c.c. of the solution contains the alcohol-ammonia-soluble constituents from the suspended matter contained in 20 c.c. of Wine of Cardui.

Acid-Precipitable Substances.—The filtrate from which the suspended matter had been removed was evaporated to small volume to remove alcohol, and the residue diluted with water to about 1 liter. Diluted hydrochloric acid was added to this solution until no further precipitation took place. The mixture was allowed to stand over night, the precipitate collected on a paper filter, washed with a little acidified water, the washed precipitate dissolved in water containing a little ammonia and filtered. The solution was diluted with alcohol and water to make a volume that would contain 20 per cent. of alcohol. One c.c. of the solution contains the acid-precipitable substances from 8 c.c. of Wine of Cardui.

Alcohol-Precipitable Substances.—The filtrate from the acid-precipitable substances was neutralized with ammonia water, evaporated to small volume, and poured into about five volumes of slightly acidified alcohol. The mixture was allowed to stand over night, the precipitate collected in a Gooch crucible, washed with alcohol, and dissolved in water containing a little ammonia. The solution was diluted with alcohol and water to make a volume that would contain 20 per cent. of alcohol. One c.c. of the solution contains the alcohol-precipitable substances from 8 c.c. of Wine of Cardui.

Ether-Soluble Substances.—The filtrate from the alcohol-precipitable separation was evaporated to small volume to remove alcohol, and the residue shaken several times with ether. The ethereal solutions were washed with water, allowed to evaporate spontaneously and the residue taken up in 70 per cent. alcohol. One c.c. of the solution contains the ether-soluble substances from 20 c.c. of Wine of Cardui.

Ethyl Acetate-Soluble Substances.—The solution which had been shaken with ether was evaporated somewhat to remove the organic solvent, and shaken with several successive portions of washed ethyl acetate. The several portions of solvent were united, evaporated on the steam bath by the aid of a fan, and the residue as finally obtained taken up in 70 per cent. alcohol. One c.c. of the solution contains the ethyl acetate-soluble portion from 20 c.c. of Wine of Cardui.

Extraction of Viburnum Prunifolium (and other Drugs) by the Stas-Otto Method

A portion of an authenticated specimen (*Viburnum prunifolium*, U. S. P. VIII, 250 gm.) was macerated for forty-eight hours with 250 c.c. of alcohol which had been slightly acidified with tartaric acid. The macerate was then packed in a percolator and percolated with 95 per cent. alcohol until exhausted. The percolate was allowed to evaporate spontaneously to some extent and the evaporation then continued on a slowly simmering steam bath until a soft, molasses-like residue remained. This was triturated with about 800 c.c. of water, and the mixture allowed to stand over night. The supernatant liquid was then decanted through a filter, the precipitated resin dried in the air, the residue massed with kaolin, the mass divided and placed in 124 capsules. Each capsule, therefore, contains the resin-like substances from 2 gm. of *Viburnum prunifolium* (Package 1).

The aqueous liquid which had been decanted from the precipitated resins was placed in a separator and repeatedly shaken with 250 c.c. portions of ether. The united ether extracts were washed with water, allowed to evaporate spontaneously, the residue taken up in a few cubic centimeters of neutral alcohol, the solution filtered, and the filtrate made up to 25 c.c. with the solvent. Each cubic centimeter of the alcohol solution, therefore, contains the ether-soluble constituents of 10 gm. of *Viburnum prunifolium* less the constituents removed by previous manipulations (Package 2).

The faintly acid, aqueous solution which had been shaken with ether was then made alkaline with potassium hydroxid solution, and the solution further shaken with several 250 c.c. portions of ether. The ether was allowed to evaporate spontaneously, the residue (which was very small) taken up in a little alcohol, the solution filtered, and the filtrate made up to 25 c.c. with more of the solvent. Each cubic centimeter of the alcoholic solution, therefore, contains the ether-soluble constituents of 10 gm. of *V. prunifolium* less the constituents removed by previous manipulations (Package 3).

Some solid ammonium chlorid was then added to the aqueous solution which had been shaken with ether, and the solution again shaken with ether. The ethereal layer was removed, washed with water, and allowed to evaporate spontaneously. Practically no residue was obtained. The addition of ammonium chlorid caused no precipitation in the solution.

The solution was then shaken with several 100 c.c. portions of amylic alcohol, the solvent removed, washed with water and evaporated on a steam bath, a fan being used to facilitate the evaporation. The residue was taken up in a little alcohol, the solution evaporated to dryness, the residue taken up in alcohol, the solution filtered, and the filtrate made up to 25 c.c. with alcohol. Each cubic centimeter of the alcoholic solution, therefore, contains the amylic alcohol-soluble constituents of *V. prunifolium* not removed by the previous manipulations (Package 4). An odor of amylic alcohol persists.

The aqueous solution which had been shaken with amylic alcohol was faintly acidified with hydrochloric acid, some powdered glass added and the solution evaporated to dryness on the steam bath. The residue was screened through a No. 40 sieve, and the powder extracted with hot chloroform. The solvent was evaporated on the steam bath in a current of air from a fan, the residue (which was insignificant) taken up in a little alcohol, the solution filtered, and the filtrate made up to 25 c.c. with alcohol. Each cubic centimeter of the alcoholic solution contains, therefore, the chloroform-soluble constituents of *V. prunifolium* not removed by previous manipulation (Package 5).

The above described process was duplicated on 250 gm. of an authenticated specimen of *Viburnum opulus*, U. S. P. VIII, and the fractions obtained labeled in accordance with the fact.

The extractives from both drugs were then sent to Dr. Worth Hale of the Harvard Medical School for pharmacologic tests. After exhaustive tests on dogs, cats and guinea-pigs, pregnant and otherwise, Dr. Hale reported that "*Viburnum prunifolium* has no uterine effect in any ordinary dose." On the other hand, *Viburnum opulus* produces a slight contraction of the uterus, the effect on the virgin uterus of the guinea-pig being about one-one hundredth as strong as a corresponding dose of fluidextract of ergot.

Determination of Extractives in Viburnum Prunifolium (Bark of Stem and Root) with Alcohol of Different Strengths

A weighed quantity of the bark of the steam of *Viburnum prunifolium* was moistened with a small quantity of 20 per cent. alcohol, the drug allowed to macerate for two hours, the mixture packed in a percolator, covered with the menstruum (20 per cent. alcohol), and the mixture allowed to macerate for forty-eight hours. The drug was then percolated to practical exhaustion with more of the menstruum, the percolate

evaporated to dryness, and the residue dried at 100 C. and weighed. From 10 gm. of the bark a residue weighing 2.4153 gm. was obtained, equivalent to 24.15 per cent. of extractive.

The above described process was duplicated, the bark of the root of *Viburnum prunifolium* being used. From 10 gm. of this bark a residue of 1.4582 gm. was obtained, equivalent to 14.58 per cent. of extractive.

The marc in each of the percolators was then percolated with 63.2 per cent. alcohol (alcohol two volumes, water one volume) to practical exhaustion, and the respective percolates evaporated to dryness, and the residue dried at 100 C. and weighed.

The residue from the bark of the stem weighed 0.1463 gm., equivalent to 1.46 per cent. of extractive.

The residue from the bark of the root weighed 0.3106 gm., equivalent to 3.11 per cent. of extractive.

The marc in the percolators was then percolated with 71.2 per cent. alcohol (alcohol three volumes, water one volume) to practical exhaustion, and the respective percolates evaporated to dryness, and the residues dried at 100 C. and weighed.

The residue from the stem bark weighed 0.1310 gm., equivalent to 1.31 per cent. of extractive.

The residue from the root bark weighed 0.0532 gm., equivalent to 0.53 per cent. of extractive.

The marc in each of the percolators was then extracted with 95 per cent. alcohol to exhaustion, the percolates evaporated to dryness separately, and the residues dried at 100 C. and weighed.

The residue from the stem bark weighed 0.6539 gm., equivalent to 6.54 per cent. of extractive.

The residue from the root bark weighed 0.5816 gm., equivalent to 5.82 per cent. of extractive.

The entire extractive from the stem bark (10 gm.) weighed 3.3465 gm., equivalent to 33.47 per cent.

The entire extractive from the root bark (10 gm.) weighed 2.4036 gm., equivalent to 24.04 per cent.

The several results found are summarized in the following table; the quantities shown having been calculated for 100 gm. of drug:

VIBURNUM PRUNIFOLIUM

Drug	20% Alc.	3.2% Alc.	71.2% Alc.	95% Alc.	Total extractives
Stem bark....	24.15	1.46	1.31	6.54	33.46
Root bark....	14.58	3.11	0.53	5.82	24.04

Resin from Viburnum Prunifolium Extracted by 20 per cent. Alcohol (Bark from the Stem and Bark from the Root)

The viburnum resins (or substances appearing in the examination where resins would be expected) which were soluble in 20 per cent. alcohol were determined separately in a weighed portion of the stem bark of *Viburnum prunifolium*, and of the root bark from the same plant. The method used is as follows:

"A weighed quantity (20 gm.) of the bark was macerated for twenty-four hours with 100 c.c of 20 per cent. alcohol. The mixture was filtered and the insoluble portion and its container as well as the filter washed with sufficient 20 per cent. alcohol to make the total volume of the filtrate to 100 c.c. The filtrate was evaporated to about 10 c.c. and the residue poured into 90 c.c. of cold water which had been slightly acidulated with hydrochloric acid. The precipitate was collected on a filter, partially dried, and dissolved so far as possible in 95 per cent. alcohol. The filtered solution was evaporated to small volume and the residue poured into 90 c.c. of cold water which had been slightly acidulated with hydrochloric acid. After twenty-four hours the precipitate was collected in a weighed Gooch crucible, dried at 100 C. to constant weight and weighed."

The weight obtained from 20 gm. of the stem bark was 0.0178 gm., or 0.089 per cent.; that from 20 gm. of the root bark was 0.0656 gm., or 0.328 per cent.

The material so obtained was insoluble in 20 per cent. alcohol, but somewhat soluble in dilute ammonia water. It was also soluble in 95 per cent. alcohol. This material did not have the usual properties of resins, but appeared to be in the nature of a vegetable acid, like glycyrrhizic acid. It is probably apothem.

Solubility of the Resins from Viburnum Prunifolium (Bark of Stem)

A weighed portion (20 gm.) of *Viburnum prunifolium*, stem bark, was extracted with 95 per cent. alcohol by maceration for seventy-two hours with 100 c.c. of the solvent. The mixture was filtered, and the residue washed with 100 c.c. of the fresh solvent. The filtrates were united, evaporated to small volume, and an attempt made to precipitate the resins from the solution by mixing with a large excess of water. The resins did not separate well. In consequence a small quantity of ammonia water was added to the aqueous mixture, after which the solution was acidified slightly with hydrochloric acid and the mixture containing the precipitate was allowed

to stand over night. The supernatant liquid was decanted through a weighed Gooch crucible with the least possible disturbance of the precipitate, the precipitate washed with water, and the wash water decanted through the crucible. The residue of resins or resin-like substances was then macerated with 100 c.c. of 20 per cent. alcohol for twenty-four hours with occasional stirring and shaking. After standing until the precipitate had settled, the supernatant liquid was decanted through the weighed Gooch crucible mentioned above, the residue again treated with 100 c.c. of the fresh solvent, the mixture decanted as before, the filtrates united, the solutions evaporated to dryness, and the residue dried at 100 C. and weighed. From 20 gm. of drug a residue of 0.0941 gm. was obtained, equivalent to 0.47 per cent. Since the total resins of the drug were not determined, the *percentage* of resins or resin-like substances which were soluble in 20 per cent. alcohol as calculated from the entire weight of drug taken has but little significance.

The residue of resins of resin-like substances insoluble in 20 per cent. alcohol was macerated with 63.2 per cent. alcohol (alcohol, two volumes, water, one volume) for twenty-four hours with occasional stirring and shaking. After the precipitate had settled, the supernatant liquid was decanted through the weighed Gooch crucible described above with the least possible disturbance of the precipitate, and the precipitate washed with 100 c.c. of the menstruum by stirring and shaking as described above. After the precipitate had settled, the supernatant liquid was decanted through the above mentioned crucible with the least possible disturbance of the precipitate, the filtrates united, the solution evaporated to dryness, and the residue dried at 100 C. and weighed. From 20 gm. of the drug a residue weighing 0.1192 gm. was obtained, equivalent to 0.6 per cent.

The residue of resins or resin-like substances insoluble in 63.2 per cent. alcohol was then macerated with 100 c.c. of 95 per cent. alcohol with stirring and shaking as described above. After standing, the supernatant liquid was decanted through the weighed Gooch crucible mentioned above, the residue of resins or resin-like substances washed with 100 c.c. of 95 per cent. alcohol, and the insoluble residue collected in the above mentioned crucible, dried at 100 C. and weighed. The filtrate was evaporated to dryness, and the residue dried at 100 C. and weighed. The residue of resins soluble in 95 per cent. alcohol from 20 gm. of the drug weighed 0.5212 gm., equivalent to 2.61 per cent. The insoluble material in the

Gooch crucible (insoluble in 95 per cent. alcohol) weighed 0.3784 gm., equivalent to 1.89 per cent.

The results obtained are shown in the following table, the quantities shown having been calculated for 100 gm. of drug.

STEM BARK OF VIBURNUM PURIFOLIUM

Soluble in 20% alcohol	Soluble in 63.2% alcohol	Soluble in 95% alcohol	Insoluble in 95% alcohol	Total
0.4705 gm.	0.596 gm.	2.606 gm.	1.892 gm.	5.5645 gm.

These results show that of the total resin-like material obtained from the stem bark of *Viburnum prunifolium*, 8.45 per cent. was soluble in 20 per cent. alcohol, 10.71 per cent. was soluble in 63.2 per cent. alcohol, 46.83 per cent. was soluble in 95 per cent., and 34.0 per cent. was insoluble in 95 per cent. alcohol. The portion insoluble in 95 per cent. alcohol was not soluble in water, but was slightly soluble in ammonia water.

LEAD IN "AKOZ"

Akoz is a mineral product sold by the Natura Company of San Francisco, and said to possess most remarkable medicinal properties.

A circular issued by the Natura Company begins thus:

"While scientists have been striving through the centuries to compound remedies for man's various ills, Nature, greatest chemist of them all, has been working wonders in her crucibles and has achieved results far beyond man's greatest expectation."

"Nature's chief handicap has been the difficulty of placing her gifts in the hands of those whom she would benefit. By accident or fate, as you will, one of Nature's greatest medicinal products has just been discovered. It is the mineral given the name of Akoz by John D. Mackenzie, president and manager of the Natura Company of San Francisco, which is now giving this rare remedy of Nature to the public."

The circular then describes how the power of the "rare remedy" to cure rheumatism is claimed to have been discovered and asserts that:

"Akoz was subjected to every known scientific test before being presented to the public. It was practically determined that the ore contained a new element having radium-like qualities but containing nothing poisonous or harmful."

"After the curative virtues of Akoz for rheumatism, stomach trouble, eczema, catarrh, piles, ulcers and numerous other ailments had been fully established in chemical laboratory, hospital clinic, and the private practice of physicians in various parts of the world, Mr. Mackenzie effected the organization of the Natura Company."

This product, put up in the form of "Akoz Medicinal Mineral Water, Akoz Ointment, Akoz Powder and Akoz Suppositories," was submitted to the Council on Pharmacy and Chemistry for consideration some years ago with the claims that "Akoz" itself consists essentially of zinc sulphid, barium sulphate and aluminium oxid. The submitted analysis did not declare the presence of lead or of uranium though "special tests" for the latter had been "run." Without checking the claimed composition, the Council at that time refused recognition to Akoz because there was no evidence submitted for the very extravagant and altogether improbable therapeutic claims.

After the Council had concluded the consideration of Akoz a letter was received from a California physician stating that according to an analysis submitted to him Akoz contained 0.34 per cent. of lead in the form of lead sulphate. The correspondent held that, while the lead sulphate did not pass into solution, persons drinking the supernatant liquid from Akoz (the "medicinal mineral water" is made by adding Akoz to ordinary water) might inadvertently swallow some of the powder. He was inclined to believe that this might account for a case of lead poisoning which had been observed in a patient who had been taking Akoz.

Inasmuch as it has been demonstrated by Carlson and Woelfel (Carlson, A. J., and Woelfel, A.: Solubility of Lead Sulphate and Basic Lead Carbonate in Human Gastric Juice. . . . In Hygiene of the Painter's Trade by Alice Hamilton, Bull. of U. S. Bureau of Labor Statistics No. 120, May 13, 1913, pp. 22-32) that even small quantities of lead sulphate, when taken into the system for a long time, have produced lead poisoning, the laboratory deemed it important that the products be examined for lead.

A specimen of "Akoz Powder" submitted to the Council by the Natura Company and contained in a sifter-top can was taken for analysis. The contents of the can were thoroughly mixed. To determine the presence of lead some of the powder was extracted with ammonium acetate solution.

Details of Analysis

Qualitative tests showed the presence of lead and sulphate in the ammonium acetate solution.

The presence of lead was demonstrated by the black precipitate with hydrogen sulphid, the yellow precipitate with potassium chromate and the typical yellowish crystalline precipitate with potassium iodid.

The presence of sulphates in the ammonium acetate solution was shown by the formation of a precipitate with barium chlorid solution and acetic acid.

Two 2 gm. samples (A and B) were taken for the quantitative determination of lead. Each was treated repeatedly with a saturated solution of ammonium acetate until the filtered ammonium acetate solution gave no appreciable precipitate with potassium chromate solution. The ammonium acetate extractions from each specimen were combined and treated with hydrogen sulphid, the precipitated lead sulphid filtered off and washed, and ignited with sulphuric acid at a low heat. The crucible with the residue of lead sulphate was cooled and weighed.

A yelded 0.0469 gm., or 2.34 per cent., lead sulphate.

B yielded 0.0440 gm., or 2.20 per cent., lead sulphate.

While the laboratory has no evidence to show that the amount of lead sulphate thus found to be present is likely to prove harmful, the following cautionary letter was sent to the Natura Company:

"According to information which you sent to the Council on Pharmacy and Chemistry your product "Akoz" does not contain lead. In view of reports received ascribing symptoms, resulting from the internal use of Akoz, to chronic lead poisoning, an examination of a specimen of Akoz Powder, which you sent to the Council, was made. This examination indicates the presence in Akoz Powder of about 2.2 per cent. lead sulphate. In view of the disastrous results likely to follow the internal use of products containing even small amounts of lead, the above is submitted to you for your consideration."

No reply to the foregoing was received from the Natura Company.

SODIUM ACETATE IN WARMING BOTTLES

Recently the laboratory's attention was called to the "ThermoR Waterless Hot Bottle," manufactured by the Royal Thermophor Sales Co., New York. The following claims appear in one of the advertising pamphlets:

"There is moist heat". "Rubber hot-water (? ? ?) naturally give a *moist* heat." It (ThermoR) gives a *dry* heat.

"The 'THERMOR' Bottle is *not* a hot-water bottle—it acts on a principle that is entirely different and new."

". . . gives you *first, last and all the time* a fixed degree of dry usable heat—a heat that holds steadily at 125 degrees for fully twelve hours—you will easily see why it is that 'THERMOR' relieves and cures where hot-water bottles fail."

The bottle was nickel plated, 8⅜ inches in diameter and 1½ inches thick, and in appearance resembled an exaggerated closed Ingersoll watch.

The bottle is not flexible and weighs 3½ pounds. The contents consisted essentially of sodium acetate. This salt melts when heated. When it cools the temperature inside the bottle is relatively constant, as it will remain at the "freezing point" until all of the sodium acetate has solidified. The duration of the time that it remains warm when well wrapped is simply in inverse proportion to the conductivity of the surrounding environment. When two ordinary towels were carefully arranged about it, the air between the bottle and the wrappings was maintained at a temperature of 40-50 C. (104-122 F.) for a period of eight hours.

The company's implication that the heat given out by the Thermor bottle differs from that given out by an ordinary hot-water bottle is an absurdity. The use of sodium acetate in the preparation of warming bottles has been in practice many years, and is not "a principle that is entirely different and new." Furthermore the therapeutic claims are extravagant.

ANTI-SYPHILITIC COMPOUND (SWEENY)

A specimen of Anti-Syphilitic Compound (Sweeny), sold by The National Laboratories of Pittsburgh, was received from a physician. The package (1 ounce size) has been opened by the sender and about three fourths of the contents removed.

From the rather indefinite statements in the literature of the manufacturer it is gathered that the preparation is claimed to be a "sterile, oily emulsion" which contains $\frac{1}{20}$ grain of mercuric benzoate in each 5 minims, together with some sodium chlorid. According to information furnished by the Laboratory's correspondent, the price asked for the preparation is $15 an ounce.

The quantity of the preparation received was too small to permit a complete examination, but, from the tests which it was possible to make, the preparation appears to be an aqueous solution containing some suspended matter and small quantities of mercuric benzoate and a chlorid, presumably sodium chlorid. There was no evidence of the presence of an "oily emulsion." Quantitative tests indicated the presence of a mercuric salt, equivalent to about 0.2783 gm. of crystallized mercuric benzoate per 100 c.c. This corresponds to about 0.00086 gm. in each 5 minims, or about 26.5 per cent. of the amount claimed.

A HAWAIIAN "CONSUMPTION REMEDY"

An inquiry from Honolulu, H. T., with regard to a medicine for pulmonary tuberculosis, was referred to the Chemical Laboratory. A specimen sent by the inquirer was labeled as a prescription of Dr. T. Uemura, a Japanese, by whom it was said to be prepared. According to the correspondent who sent it in, the substance was sold for $1 a bottle. It was used in conjunction with another which was injected hypodermically at a cost of $15 for every hypodermic dose injected.

Qualitative examination indicated that the liquid was a solution of sodium benzoate (quantitatively determined as 5 per cent.) in water and that it was free from other potent ingredients. It contained a trace of iron.

Details of Analysis

Benzoate.—A portion was acidified with sulphuric acid and extracted with several portions of ether. The ether extractions were united, washed with water, the other solution allowed to evaporate spontaneously and the residue dried over sulphuric acid. The residue thus obtained was identified as benzoic acid thus: The melting point of the residue was 121-122 C., uncorrected (benzoic acid melts at 122 C.). A portion of the residue was converted to the paratoluid according to the method of Mulliken (Mulliken's Identification of Pure Organic Compounds, vol. 1) and was found to melt at 153 C., uncorrected (according to Mulliken the melting point for benzoparatoluid is 155 C., uncorrected). The solution of the residue in hot water gave the characteristic flesh-colored precipitate of ferric benzoate on the addition of ferric chlorid test solution. On sublimation of a portion of the residue the characteristic odor of benzoic acid was observed. Then the

residue was warmed with alcohol and strong sulphuric acid the characteristic odor of ethyl benzoate was observed.

Absence of Alkaloids.—A portion of the original liquid was made alkaline with ammonia water, extracted with chloroform and the chloroform allowed to evaporate spontaneously. The dish from which the chloroform had evaporated was treated with a few cubic centimeters of normal sulphuric acid and the acid liquid tested with the usual alkaloidal reagent. The negative results indicated the absence of alkaloids. To confirm the absence of alkaloids, 5 c.c. of the original liquid was acidified with sulphuric acid, the precipitated benzoic acid filtered off, and the filtrate tested for alkaloids by means of the usual alkaloidal reagents. The results were negative.

Quantitative Determination of Sodium Benzoate.—Ten c.c. of the original liquid was evaporated and the residue dried at 100 C. The residue weighed 0.5067 gm. Ten c.c. of the original liquid was acidified with sulphuric acid and extracted with several portions of ether, the ether was washed with water, then allowed to evaporate spontaneously and the residue dried to constant weight over sulphuric acid. The residue (benzoic acid) weighed 0.4268 gm. This is equivalent to 0.5058 gm. sodium benzoate. The aqueous solution remaining after the extraction of the benzoic acid was evaporated to dryness, the excess of sulphuric acid driven off and the residue heated to constant weight with the usual precautions. The weight of this residue of sodium sulphate was 0.2475 gm., which is equivalent to 0.5021 gm. sodium benzoate (this residue contained a trace of iron salt). To prove that this residue was sodium sulphate, its sulphate content was determined. The barium sulphate obtained in the regular way weighed 0.41 gm., equivalent to 0.2495 gm. sodium sulphate.

BINIODOL

Biniodol is marketed by Charles C. Yarbrough of Memphis, Tenn. According to the advertising it is "A REAL One Per-cent. Solution of STRAIGHT Red Mercuric Iodide (Mercury Biniodide) in Aseptic Vegetable Oil." In an application to the Council on Pharmacy and Chemistry for the admission of Biniodol to New and Nonofficial Remedies the presence of "about three-fourths of one percent." of "chemically pure guaiacol," added for "its local anesthetic effects," was declared by the manufacturer.

Biniodol is marketed with claims which carry the impression that it is new and superior to other oil solutions of mercuric iodid, thus:

"A new preparation of mercury has, however, been devised which admirably meets the requirements of intramuscular injection. It is Biniodol . . .

"No untoward results have ever been known to follow the use of Biniodol.

". . . is an ideal mercurial injection. It is perfectly clear, is practically painless, . . . and never produces abscess."

The Council on Pharmacy and Chemistry requested this laboratory to examine the claims made in regard to the composition and, with a view of subjecting the claims of superiority to a clinical trial, to prepare two solutions of mercuric iodid in oil; one to contain the same proportions of mercuric iodid and guaiacol as is contained in Biniodol and the other to contain the same proportion of mercuric iodid but no guaiacol.

Biniodol, as submitted to the Council by the manufacturer, was a light colored oil having a strong odor resembling that of guaiacol. Qualitative tests indicated the presence of mercuric iodid, guaiacol and a fatty oil and the absence of alkali, iodids and petrolatum. The followinng data were obtained:

Optical rotation in a 1 dm. tube at 20 C.....	1.36°
Refractive index of the fatty oil (at 24 C.) (after the removal of guaiacol)	1.4750
Iodin absorption number of oil (after removal of guaiacol) 114	
Melting point of the fatty acids obtained from the oil...20-21C.	
Total phenols (calculated as guaiacol).....	2.48 per cent.
Mercuric iodid (calculated from mercuric sulphid)....	1.01 per cent.
Mercuric iodid (calculated from total amount of iodin).	1.03 per cent.

From the above it was concluded that Biniodol essentially is a one per cent. mercuric iodid solution in a relatively unsaturated fatty oil (probably a mixture of castor oil and poppy seed oil), containing about 2.5 per cent. of guaiacol, and not 0.75 per cent. of guaiacol as claimed.

On the basis of the analysis of Biniodol synthetic solutions were prepared according to the methods as given below:

A mixture of 340 gm. of castor oil with 660 gm. of poppy seed oil was prepared. Two portions of this mixture (495 gm. and 482 gm., respectively) were weighed. To each of these 5 gm. of mercuric iodid were added, the oil placed on the

water bath at about 60 C. and agitated by passing through a current of dry air. After all except a few particles of the mercuric iodid had dissolved, the agitation was stopped and, after cooling, 12.5 gm. of guaiacol were added to the second solution. After standing a short time, it became evident that it would be necessary to filter the liquids to remove undissolved mercuric iodid and foreign matter. The exposure to the air during the filtration of the second solution evidently caused a loss of guaiacol. This is not surprising if the length of time necessary for the filtration of such a viscous liquid be considered. An assay demonstrated the presence of only 2.3 per cent. of guaiacol in the second solution. The guaiacol content of the second solution was accordingly brought up to 2.6 per cent. by the addition of more guaiacol. The two filtered solutions were then placed in 1-ounce bottles, the containers stoppered and sterilized by heating to 100 C. for two hours.

As the preparation of these solutions made it necessary that they stand exposed to the air for some time, the amount of guaiacol in each of the finished preparations was determined and these results were compared with the amount of guaiacol in a specimen of Biniodol recently purchased from the manufacturer, which specimen was to be used in the clinical comparisons. The mercuric iodid content of the two solutions was also checked by analysis. The results were:

	Mercuric iodid %	Guaiacol %
Solution 1. (Mercuric iodid without guaiacol)	1.07	
Solution 2. (Mercuric iodid with guaiacol)	1.05	2.3
Biniodol (New lot)	2.60	

The Laboratory's findings concerning the guaiacol content of Biniodol were submitted to Charles C. Yarbrough. He expressed surprise that in his statement to the Council, Biniodol had been claimed to contain only 0.75 per cent. of guaiacol; that he believed it to contain about 2.75 per cent. and that it had been his intention to declare this amount of guaiacol in the statement to the Council.

The clinical trials having shown the manufacturer's claims of superiority to be unfounded, the Council advised the manufacturer that Biniodol was an unessential modification of an established nonproprietary article and therefore ineligible for New and Nonofficial Remedies.

Details of Analysis

Mercuric Iodid.—A portion of the sample was shaken with repeated small portions of alcohol until all of the mercuric iodid had been removed from the oil, as was shown by the fact that the final alcoholic shakeout gave no precipitate with hydrogen sulphid. A few drops of concentrated hydrochloric acid were then added to the combined alcoholic solution and the whole saturated with hydrogen sulphid. The liquid was allowed to stand for a few hours to allow the precipitate to become denser. The mercuric sulphid was then collected in a weighed Gooch crucible, washed several times with alcohol, then twice with ether and dried a few minutes at 100 C. and weighed.

A weight of 4.147 gm. of Biniodol yielded 0.0213 gm. of mercuric sulphid, equivalent to 0.0417 gm. of mercuric iodid, or 1.01 per cent.

Total Iodin.—In determining total iodin, a sample was saponified with alcoholic potassium hydroxid, and the mixture filtered to remove precipitated mercuric oxid. The filtrate was then evaporated to dryness in a porcelain dish, the residue heated to carbonization, the charred mass leached out with hot water, the leachings filtered, the alkaline filtrate acidified with nitric acid, the iodid precipitated by silver nitrate and the silver iodid collected, dried and weighed in the usual way. A control was run on the amount of alcoholic potassium hydroxid used to ascertain the amount of halogen present in it.

A weight of 9.338 gm. of the material gave 0.1029 gm. of silver iodid; the control 0.0033 gm.; $0.1029 - 0.0033 = 0.0996$ gm. of silver iodid derived from the Biniodol, equivalent to 0.0965 gm. of mercuric iodid, or 1.03 per cent.

Guaiacol.—A sample of Biniodol was distilled with steam until the distillate no longer had an appreciable phenolic odor. About 125 c.c. were collected. The distillate was then subjected to the hypobromite process for the determination of phenol.

The guaiacol was separated by this process from a preparation of similar oils containing a known amount of guaiacol, and subjected to the same analytical process. The amount of guaiacol present in Biniodol was deduced by a comparison of these results with those obtained from Biniodol.

The distillate from 4.151 gm. of Biniodol consumed hypobromite solution equivalent to 43.6 c.c. of tenth-normal sodium

thiosulphate. The distillate from a sample of oil containing 0.0620 gm. of guaiacol consumed hypobromite solution equivalent to 26.27 c.c. of tenth-normal sodium thiosulphate. The distillate from a sample of oil containing 0.0620 gm. of guaiacol consumed 26.27 c.c. of tenth-normal sodium thiosulphate. Hence 1 c.c. of the thiosulphate solution is equivalent to 0.00236 gm. of guaiacol. The above sample of Biniodol contained 0.1029 gm. of phenols calculated as guaiacol or 2.48 per cent.

Constants of the oil used.—After the guaiacol and most of the mercuric iodid had been removed by steam distillation, the oil was separated and dried by filtering through a dry filter in a 100 C. oven and then used for the determination of its constants.

Refractive Index.—This was taken with an Abbe refractometer at 24 C.; value found, 1.4750.

Iodin absorption number.—This was determined by the Hanus method as given in Bureau of Chemistry Bulletin No. 107, p. 136.

A weight of 0.2455 gm. of the oil, treated with 25 c.c. of Hanus' solution, consumed iodin equivalent to 22.10 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.2806 gm. of iodin. This is equivalent to an iodin absorption number of 114.3 for the oil. A weight of 0.2135 gm. of the oil, after treatment with 25 c.c. of Hanus' solution, consumed iodin equivalent to 19.11 c.c. of tenth-normal sodium thiosulphate, or 0.2426 gm. of iodin. The iodin number found for the oil was 113.6.

In order to duplicate Biniodol an oil must be found capable of dissolving 1 per cent. of mercuric iodid and whose chemical constants correspond closely to those found in the above analysis.

The constants of corn oil are very nearly the same as those of the oil in Biniodol but its color is a much deeper yellow than that of Biniodol and if saturated with mercuric iodid will dissolve about only 0.8 per cent. Mixtures of castor oil and olive oil, or of castor oil and sesame oil would dissolve 1 per cent. or more of mercuric iodid but the iodin absorption number of such mixtures would be much lower than that found for the oil in Biniodol.

Lemaire (Repert pharm. XXI, 97-102, through C. A. 1909, p. 1444; see Journal A. M. A., Dec. 19, 1914, p. 2247) describes

the preparation of a 1 per cent. solution of mercuric iodid in a mixture of poppy seed and castor oils with the addition of three grams of guaiacol per 100 c.c.

A mixture of one part of castor oil and two parts of poppy seed oil was prepared. The constants of this mixture were found to correspond closely to those of the oil used in Biniodol. The optical rotation observed in a 1 dm. tube at 21 C. was 1.28°. The iodin absorption number was determined by the Hanus method as above described. A weight of 0.2563 gm. of the material absorbed iodin equivalent to 23.57 c.c. of tenth-normal sodium thiosulphate, or 0.2992 gm. of iodin, equivalent to an iodin absorption number of 116.7. A weight of 0.2315 gm. of Biniodol absorbed iodin equivalent to 21.10 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.2678 gm. of iodin, corresponding to an iodin absorption number of 115.7.

A portion of the mixture of oils was then saturated with mercuric iodid at about 80 C., the mixture cooled, filtered and the mercuric iodid determined in a portion by the method used with Biniodol. A weight of 7.188 gm. of the material yielded 0.0489 gm. of mercuric sulphid equivalent to 0.0956 gm. of mercuric iodid, or 1.33 per cent.

Thus it appears that a preparation essentially the same as Biniodol can be obtained by preparing a 1 per cent. solution of mercuric iodid in a mixture of one part of castor oil and two parts of poppy seed oil and adding 2.5 per cent. of guaiacol.

Accordingly there were prepared for clinical purposes (a) a 1 per cent. solution of mercuric iodid in the mixture of oils mentioned without guaiacol, and (b) a 1 per cent. solution of mercuric iodid in the oils mentioned but containing also 2.5 per cent. of guaiacol.

Imitation "Biniodol."—(a) The steam distillate from 2.137 gm. of the material required hypobromite solution equivalent to 21.08 c.c. of tenth-normal sodium thiosulphate (1 c.c. of which was found to be equivalent to 0.002336 gm. of guaiacol). This is equivalent to 0.0492 gm. of guaiacol, or 2.30 per cent. (b) The distillate from 2.811 gm. of material required hypobromite solution equivalent to 26.86 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.0627 gm. of guaiacol, or 2.23 per cent.

From these analyses it is apparent that the preparation designated "imitation Biniodol" has lost about 0.2 per cent.

of guaiacol. To the mixture 0.3 per cent. of guaiacol was added and after mixing, the preparation was reassayed. (a) The distillate from 2.737 gm. of the material required hypobromite solution equivalent to 30.89 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.0721 gm. of guaiacol, or 2.63 per cent. (b) The distillate from 2.328 gm. of the material required hypobromite solution equivalent to 26.08 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.0610 gm. of guaiacol or 2.62 per cent.

Mercuric Iodid.—The mercuric sulphid obtained from 7.9841 gm. of the material by the process described above weighed 0.0428 gm., equivalent to 0.0836 gm. of mercuric iodid or 1.05 per cent.

One per cent. solution of mercuric iodid in oil, without guaiacol.—A weight of 9.320 gm. of material yielded 0.0512 gm. of mercuric sulphid, equivalent to 0.1000 gm. of mercuric iodid, or 1.07 per cent.

"Biniodol" (a second lot to be used for clinical tests). The steam distillate from 3.153 gm. of material required hypobromite solution equivalent to 34.39 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.0802 gm. of guaiacol, or 2.54 per cent. (b) The distillate from 3.181 gm. of material required hypobromite solution equivalent to 35.49 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.0828 gm. of guaiacol, or 2.60 per cent.

"FRONTIER ASTHMA REMEDY" (H. C. TREATMENT FOR ASTHMA)

One original bottle of "H. C. Treatment for Asthma," manufactured by the Frontier Asthma Co., Buffalo, N. Y., was submitted to the Chemical Laboratory for examination. The label on the bottle was partly printed and partly written in by hand as follows, words in italics representing the hand-written portions:

"H. C. Treatment for Asthma."
"Prescribed for *W. H. Whitlow.*
"By Dr. *Wilson*
"In consultation with Dr. *Calkins.*
"Directions: *Take 30 drops in 1/4 glass of water 3 times a day after meals and 60 drops on retiring.*"
"Prescription No. *x 105751.*"
"Do not change the dose unless by special order. Use dropper to measure dose."
"Put up at the Laboratory of FRONTIER ASTHMA CO., cor. Niagara and Hudson Sts., BUFFALO, N. Y."

The bottle contained a brown, odorless liquid, having a bitter taste. The reaction toward litmus was neutral. The specific gravity of the liquid at 15.6 C. was 1.1164. Qualitative tests demonstrated the presence of ammonia (combined form), arsenic (arsenous form), potassium, sodium, iodid and caffein. No free iodin, acetanilid, acetphenetidin, salicylates, acetylsalicylic acid, morphin or other alkaloids than caffein, or other metals than those mentioned were found.

Quantitative determinations yielded the following:

Ammonia (NH_3)	0.60	gm. in 100 c.c.
Arsenic (As^{+++})	0.038	gm. in 100 c.c.
Potassium (K^+)	1.16	gm. in 100 c.c.
Sodium (Na^+)	0.85	gm. in 100 c.c.
Iodid (I^-)	12.95	gm. in 100 c.c.
Caffein	2.27	gm. in 100 c.c.

From the results of this analysis it appears that each 100 c.c. of the solution contains essentially 5.2 gm. of ammonium iodid, 4.9 gm. of potassium iodid, 5.5 gm. of sodium iodid, 2.3 gm. of caffein and 0.05 gm. of arsenous oxid (As_2O_3). Calculating from the iodid determination, each dose (30 minims or 2 c.c., assuming that a minim dropper is used) is equivalent to 5.1 grains of potassium iodid, together with ¾ grain of caffein and 1/60 grain of arsenous oxid.

Details of Analysis

Caffein.—Twenty c.c. of the sample were measured into a separator, the solution made distinctly acid with dilute sulphuric acid and shaken with chloroform repeatedly till the caffein was completely extracted, as was shown by the fact that on evaporating a portion of the used solvent no residue appeared. Since many alkaloids other than caffein are extracted by chloroform from acid solution containing iodids, the chloroform extracts were washed twice with dilute ammonia water, the ammonia water washed with chloroform once and this chloroform added to the original used solvent. The combined chloroform solutions were shaken twice with normal sulphuric acid. The acid water was then washed once with chloroform and this chloroform added to the rest. The chloroform was then filtered through paper wet with chloroform and collected in a tared dish, the chloroform allowed to evaporate at room temperature and the residue dried in a desiccator over concentrated sulphuric acid to constant weight and weighed. The weight of the anhydrous caffein from 20 c.c. of the material was 0.4555 gm., or 2.2775 gm. per 100 c.c.

Other alkaloids.—1. Such other alkaloids as are removed from hydriodic acid solution by chloroform would be found in the acid washwater. This was tested with the usual alkaloidal reagents with negative results.

2. The original acidified solution of the sample from which the caffein had been removed as described was made alkaline with ammonia water and the mixture extracted with chloroform. The chloroform extract was then evaporated to dryness, the residue taken up in a few c.c. of dilute sulphuric acid, and tested for alkaloids with negative results.

3. Morphin was tested for on a separate portion of the sample by Buchbinder's method (Proc. Assn. Off. Agric. Chem., 1912, p. 218-9 and also 1914) with negative results.

Arsenic.—This was determined by the modified Gutzeit test as described in U. S. Bureau of Chemistry Circular No. 102, which in summary is as follows:

The sample was boiled with sulphuric and nitric acids until the organic matter was completely oxidized, and the solution then evaporated further till the excess of nitric acid was boiled off and until the fumes of sulphur trioxid appeared. The liquid was allowed to cool and a considerable excess of bromin water was added to assure the complete removal of the iodids and the oxidation of the arsenic to the form of arsenate. After removing the excess of bromin by heat the solution was diluted to about 200 c.c., tartaric acid added to prevent the coprecipitation of antimony salts, should they be present; 10 c.c. of sodium phosphate T.S. added, and, after making the solution alkaline with ammonia water, a slight excess of magnesia mixture. The heavy precipitate of magnesium ammonium phosphate carried down the arsenic quantitatively in the form of the isomorphous magnesium ammonium arsenate. This precipitate, after washing twice with dilute ammonia water, was dissolved in 10 per cent. hydrochloric acid, about 0.5 gm. potassium iodid, and 2 c.c. stannous chlorid solution (10 per cent.) added, and the whole warmed to 90-95 C. for ten minutes. The solution was then cooled to 15 C. and placed with zinc in the evolution apparatus. This consisted of a 2 ounce wide-mouth bottle closed with a one-hole rubber stopper through which passed a glass tube bent at right angles. To this was connected a calcium chlorid tube filled with cotton moistened with lead acetate solution and it, in turn, connected with a tube bent downward at right angles and ending in a capillary. This capillary tube passed to the bottom of a flask containing, in 60 c.c. of water, 5 c.c. of a

5 per cent. solution of mercuric chlorid. After the evolution of gas had ceased, the precipitate of mercurous chlorid was filtered off on a Gooch crucible, dried at 110 C. and weighed. The weight of mercurous chlorid found from 10 c.c. of the material was 0.0722 gm., equivalent to 0.0504 gm. of arsenous oxid per 100 c.c.

Iodids.—Five c.c. of the sample by precipitation with silver nitrate gave a precipitate of silver iodid weighing 1.1977 gm. This was dissolved in potassium cyanid and electrolyzed. The weight of the metallic silver obtained was 0.5483 gm., equivalent to 1.1934 gm. of silver iodid, showing that no other halid than iodin is present.

Iodids plus Arsenites.—A 5 c.c. sample was titrated with standard silver nitrate solution (of which 1 c.c. is equivalent to 0.04682 gm. of silver iodid), 25.76 c.c. being used. This is equivalent to 1.2061 gm. of silver iodid.

Silver arsenite (Ag_3AsO_3) is also precipitated in this titration. The equivalent of 0.00504 gm. of arsenic trioxid (previously determined) is 0.0179 gm. of silver iodid, and dividing by 2 (since 0.00504 gm. arsenic trioxid was obtained from 10 c.c.) equals 0.0090 gm. of silver iodid. Subtracting:

1.2061 gm. — 0.0090 gm. = 1.1971 gm. of silver iodid.

Ammonia.—Ten c.c. of the sample were made alkaline with sodium hydroxid solution, water added and the solution distilled into 50 c.c. of standardized acid solution. The excess of acid was then titrated with standardized sodium hydroxid solution. The ammonia which distilled over required for neutralization 35.43 c.c. of 0.10035 normal acid, equivalent to 0.5106 gm. of ammonium iodid (NH_4I).

Potassium and Sodium.—To 10 c.c. of the sample an excess of concentrated sulphuric acid was added and the mixture evaporated carefully to dryness, the residue ignited and weighed. The weight of the combined sulphates of potassium and sodium is 0.5231 gm. The potassium and sodium were obtained from another 10 c.c. sample in the form of chlorids and the potassium precipitated as chloroplatinate. The weight of the chloroplatinate (K_2PtCl_6) was 0.7245 gm., equivalent to 0.4948 gm. of potassium iodid (KI) or 0.2597 gm. of potassium sulphate (K_2SO_4).

The sodium sulphate in the mixed sulphates equals (0.5231 gm. — 0.2597 gm.) or 0.2634 gm., equivalent to 0.5560 gm. of sodium iodid (NaI).

No attempt was made to identify the coloring agent.

Alcohol.—A 25 c.c. sample was diluted with water to 100 c.c., and 50 c.c. distilled. The specific gravity of this distillate was 0.99982, showing that no alcohol was present.

IOCAMFEN AND IOCAMFEN OINTMENT

An original bottle of Iocamfen, manufactured by Schering and Glatz, was submitted to the Chemical Laboratory for examination. According to the label "Iocamfen . . . is produced by the interaction of Iodin, Camphor and Phenol" and contains "10% Free Iodine." The manufacturer stated to the Council that the iodin, phenol and camphor are present in the following proportions: iodin 10 per cent., camphor 70 per cent., and phenol 20 per cent.

The bottle contained a brown, viscous liquid having the odors of its constituents: camphor, phenol and iodin.

Qualitative tests demonstrated the presence of free iodin, camphor and phenol. Quantitative determinations yielded the following results:

Uncombined iodin	7.5 per cent.
Total iodin	9.3 per cent.
Camphor	66.1 per cent.
Phenol	19.7 per cent.

Details of Analysis

Iodin, Uncombined.—Uncombined iodin was determined by dissolving a weighed sample in chloroform and after the addition of very dilute potassium iodid solution, titrating with tenth-normal sodium thiosulphate. For 2.3128 gm. of Iocamfen 13 c.c. of tenth-normal sodium thiosulphate (factor 1.05) were required, equivalent to 0.1733 gm. of iodin, or 7.49 per cent.

Total Iodin.—Total iodin was determined as follows:

A portion of the material was heated with alcoholic potassium hydroxid solution in a pressure bottle for about an hour. The liquid was transferred to a porcelain dish, evaporated to dryness and the residue heated until charred. The charred mass was leached with hot water and the leachings filtered, the alkaline filtrate acidified with nitric acid and the iodid precipitated with silver nitrate solution. A control was carried out on a like quantity of alcoholic potassium hydroxid solution.

From 2.265 gm. of the material 0.3915 gm. of silver halid was obtained; the control yielded 0.002 gm. of silver halid; subtracting 0.002 gm. from 0.3915 gm. leaves 0.3895 gm. of

silver iodid obtained from the weight of Iocamfen taken; this is equivalent to 0.2105 gm. of iodin, or 9.3 per cent.

Camphor.—To approximately determine the amount of camphor present in Iocamfen, the following method was used:

A weighed portion of the material was dissolved in about 20 c.c. of carbon tetrachlorid, the solution poured into a separator, the weighing flask washed with more of the solvent and this added to the solution in the separator. An excess of sodium thiosulphate solution was added and the mixture shaken. The carbon tetrachlorid was passed through a filter, previously wetted with the solvent, into a 50 c.c. graduated flask. The thiosulphate solution in the separator was washed twice with a few c.c. of carbon tetrachlorid, the solvent added to that in the flask and the combined solution made up to 50 c.c. with more carbon tetrachlorid. The solution was placed in a 2 dm. tube, and its rotation observed at 15 C. The value found was compared with Faucon's tables in which the rotatory values for camphor in carbon tetrachlorid solution are given (Comp. rend., 1882, cliv., 652).

From 3.265 gm. of material, after treatment as above described, a rotation of 3.86 degrees at 15 C. was observed. According to the tables, this corresponds to a solution containing 2.16 gm. of camphor in 50 c.c., or 66.1 per cent.

Phenol.—This was determined as follows:

The material was placed in a flask containing an excess of sodium thiosulphate solution and the mixture distilled with steam until from 100 to 125 c.c. of distillate were obtained. The camphor was removed from the distillate by filtration and the phenol in the filtrate determined by the bromin method (U. S. P. VIII).

Material weighing 0.2455 gm. required bromin solution, equivalent to 29.42 c.c. of tenth-normal sodium thiosulphate (factor 1.05), equivalent to 0.0484 gm. of phenol, or 19.7 per cent.

From the above analysis Iocamfen appears to be a solution of iodin in the product formed by melting together two parts of phenol and seven parts of camphor, or approximately one molecule of phenol and two molecules of camphor.

If equimolecular quantities of phenol and camphor be melted together a definite compound, phenol camphor, is said to result (Leger, Bull. soc. chem., ser. 3, iv, 725). On the other hand, it has been shown by Scott (*Jour. Chem Soc.*, xcvii, 1573), that a definite compound probably is not formed if one molecule of phenol be melted with two molecules of camphor.

In view of these facts it seems probable that a mixture of the phenol-camphor compound, and uncombined camphor, is present in Iocamfen. Iodin is readily capable of direct substitution in the phenol molecule in the presence of a catalyst, e. g., mercuric oxid (Weselsky, Hlasiwetz Ber., ii,

523). Since it is a recognized fact that the effect of a catalyst is to increase the rate of a reaction only, it seems probable that the iodin in the combined state in Iocamfen is the result of the slow progress of this reaction in the absence of such a catalyst.

Along with Iocamfen the Council also requested an analysis of Iocamfen Ointment, made by Schering and Glatz. It was stated that Iocamfen Ointment contained 50 per cent. of Iocamfen in a lard-wax-cacao-butter base in proportions especially suitable for this medication. The label declared the preparation to contain "50% Iocamfen" and "5% Free Iodine."

Qualitative tests demonstrated the presence of free iodin, combined iodin, camphor, phenol, and fatty and waxy substances. Quantitative determinations gave the following results:

Uncombined iodin	0.4 per cent.
Total iodin	4.7 per cent.
Camphor	36.0 per cent.
Phenol	8.8 per cent.

Details of Analysis

The methods described in the examination of Iocamfen were used for the respective determinations in Iocamfen Ointment.

Iodin, Uncombined.—Material weighing 3.3389 gm. required 0.9 c.c. of tenth-normal sodium thiosulphate (factor 1.05), equivalent to 0.012 gm. of iodin, or 0.36 per cent. of free iodin.

Total Iodin.—Material weighing 4.6955 gm. gave 0.4089 gm. of silver halid (less control value of 0.0033 gm.) or 0.4056 gm. of silver iodid. This is equivalent to 0.2182 gm. of iodin, or 4.65 per cent. of total iodin.

Camphor.—Material weighing 3.426 gm., after treatment and solution in 50 c.c. of carbon tetrachlorid and observation at 15 C. in a 1 dm. tube gave a rotation of 1.09 degrees. According to the tables this corresponds to 1.236 gm. of camphor, or 36.2 per cent.

Phenol.—Material weighing 0.6608 gm. required bromin solution, equivalent to 35.31 c.c. of tenth-normal sodium thiosulphate (factor 1.05), equivalent to 0.0581 gm. of phenol, or 8.8 per cent. of phenol.

This analysis shows that about 90 per cent. of the iodin is in the combined state.

It is well known that iodin readily combines with fats and waxes. It is probable that most of the iodin in the ointment has combined with the fat and wax of the ointment base.

These findings having been sent to Schering and Glatz, the firm questioned the method of determining the free iodin on the ground that the immiscible solvent rendered the titration difficult. Preference was given to a method in which the titration is carried out after the substance is dissolved in 50 per cent. alcohol.

In reply the manufacturer was advised that the method had been used in the analysis of Anusol Suppositories (Rep. A. M. A. Chem. Lab., 1909, p. 32), an analysis which has not been questioned. Also that the procedure was employed by Cook for the determination of iodids in the presence of bromids and chlorids (*Jour. Chem. Soc.*, 1885, p. 471) and included in Sutton's Volumetric Analysis (7th ed., p. 201). Evidence to show that the method used in this Laboratory was faulty was also requested.

While Schering and Glatz admitted not to have any evidence to show that the method of analysis gave incorrect results, the following further experiments relative to the iodin determination and in regard to the deterioration of Iocamfen were made:

The thiosulphate solution used was standardized against twice sublimed iodin, first by the standard method given in Treadwell's Quantitative Analysis (Hall's Translation) fourth edition, 1915, p. 646, and also, in order to properly compare the titration method of Schering and Glatz, by a method in which the aqueous potassium iodid solution of the standard method is replaced by 50 per cent. alcohol as a solvent for the iodin sample and the titration made without the use of an indicator. Starch was used as an indicator in the standard method.

The difference in standard by the two methods was 0.1 per cent.

That portion of the sample of Iocamfen (liquid) which had been kept in the original brown bottle was titrated by the method used originally in which starch was used as an indicator, and by the method described by Schering and Glatz in their letter, using no indicator, thus:

"A weighed quantity of Iocamfen Liquid (approximately 3 grammes) is dissolved in from 10 to 15 times its weight of 50 to 60 per cent. alcohol, a small quantity of very dilute potassium iodid solution is added and the titration with tenth-normal sodium thiosulphate carried through to the point of decoloration."

By the original method (*a*) 2.294 gm. of the material required 13.21 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.1662 gm. of free iodin, or 7.25 per cent.; (*b*) 2.084 gm. of material required 12.05 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.1517 gm. of free iodin, or 7.28 per cent.

By the method of Schering and Glatz (*a*) 2.440 gm. of material required 13.92 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.1749 gm. of free iodin, or 7.17 per cent.; (*b*) 2.981 gm. of material required 17.39 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.2185 gm. of free iodin, or 7.33 per cent.

In Schering and Glatz' method the solution of the oily base in the 50 per cent. alcohol, after addition of an excess of sodium thiosulphate solution, has a light yellow color. This masks the end-point of the titration.

That portion of the original sample which had been kept in a transparent (white) glass-stoppered, flask about 4 feet from a large window for three months, i. e., from April 12 to July 12, was titrated by our original method only, as the amount of the sample was insufficient for checking by the Schering and Glatz' method.

(*a*) 3.148 gm. of material required 18.88 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.2376 gm. of free iodin, or 7.55 per cent.; (*b*) 2.486 gm. of material required 14.86 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.1870 gm. of free iodin, or 7.53 per cent.

The result obtained previously (three months ago) for the free iodin on this sample was 7.49 per cent. The results obtained on the sample kept in the transparent (white) flask in the light are practically the same. Those obtained on the sample kept in the brown bottle in the dark are about 0.2 per cent. lower. It would appear that the light might have a slight restraining effect on the absorption of the iodin. However, the reaction involved must have nearly reached its equilibrium before the first analysis was made.

The above findings were reported to Schering and Glatz. In reply this firm stated that its findings as to the free iodin in Iocamfen by the method of this Laboratory did not differ materially from the results obtained by its own method.

Schering and Glatz having practically admitted the correctness of the analytical data of this Laboratory and having modified its claims as to the free iodin content of Iocamfen to 7.25 per cent. the Council on Pharmacy and Chemistry admitted Iocamfen to New and Nonofficial Remedies (THE

JOURNAL A. M. A., Jan. 20, 1917, p. 199). It postponed the consideration of Iocamfen Ointment for the time, to permit the conclusion of experiments toward the development of a satisfactory ointment base by Schering and Glatz.

HYCLORITE

Hyclorite is marketed by the General Laboratories, Madison, Wis., as

"... a concentrated stabilized hypochlorite made by a new electrolytic process."

The preparation was submitted to the Council on July 29, 1915. At that time it was called "Hyclarite" and the proprietors did business as the General Purification Company.

Hyclorite, at the time called Hyclarite, was submitted with the claim that

"In each 100 grams of Hyclarite the available chlorine is equivalent to 7-7/10 grams NaOCl, sodium chloride 1 gram, and sodium carbonate 1.23 gram."

A recently issued booklet contains the statement

"Chemical composition. Hypochlorites (NaOCl) 7.7%, Salines 2.23%, Aqua 90.07%."

Determination of the "available chlorin" by the method of the U. S. P. for the valuation of chlorinated soda solution in a specimen of Hyclarite soon after its receipt from the manufacturer, indicated the presence of 3.31 gm. of "available chlorin" in 100 gm., or 3.53 gm. per 100 c.c. Since in the method of determination used each molecular weight of sodium hypochlorite present (74.46 gm.) results in the finding of one molecular weight (70.92 gm.) of "available chlorin" the 3.31 gm. of "available chlorin" found indicates the presence of 3.70 gm. of sodium hypochlorites—NaOCl—and not 7.7 gm. as claimed. This is equivalent to 1.66 gm. of chlorin actually contained in the sodium hypochlorites present. The total amount of chlorin in the specimen of Hyclorite under examination was found to be 4.4 gm. in 100 gm., or 4.69 gm. per 100 c.c. If from this amount of chlorin the amount present as sodium hypochlorite be deducted (1.66 gm.) and the remainder calculated to sodium chlorid, it is found that Hyclorite contains 4.52 gm. of sodium chlorid per 100 gm.—and not 1 per cent. as claimed in the quoted statement of composition. The recent statement of the manufacturer gives

"Salines 2.23 per cent." This figure apparently has been obtained by adding the amounts of sodium chlorid and of sodium carbonate claimed in the first statement of composition. The amounts of sodium hypochlorite and of sodium chlorid found, demonstrate not only that the manufacturer's statement of composition is incorrect, but also that these salts exist in this solution ("made by an entirely new electrolytic process") in proportions very much like the official solution of chlorinated soda. In the light of the findings of the Laboratory, it is evident that the claims quoted herewith give a false impression as to the value of Hyclorite:

"As shown by the analysis Hyclorite contains 2.23% salines. Knowing the saline content of this fluid, the physician may easily and quickly obtain an alkaline saline solution of known strength, purity and uniformity by simply diluting with water as required."

In support of the claim that Hyclorite is very stable it is asserted that:

"Tests of samples stored from one to two years under extreme conditions showed that they retainel 94% of their original strength."

This claim does not agree with the following: A specimen of Hyclorite received from the manufacturer was tested Sept. 21, 1915, and found to contain 3.31 gm. of available chlorin per 100 gm. Two portions of the liquid were placed in separate containers, one of flint and the other of amber glass, the former being about half filled and the latter completely filled, and stored in a closet to which light had access daily for short periods. A portion remaining in the original container was stored under the same conditions; so also was an unopened original bottle of Hyclorite. At the end of ten and a quarter months the fractional portions in the flint and amber glass containers assayed respectively 2.84 gm. and 2.83 gm. per 100 gm., or about 86 per cent. of the original "available chlorin"; the portion remaining in the opened original container assayed 3 gm. per 100 gm., or about 90 per cent. of the amount present at the first examination; and the contents of the previously unopened original bottle were found to assay 2.82 gm. per 100 gm., or about 85.2 per cent. of the amount which it should have contained, assuming its original strength to have been the same as that of the divided specimen. These specimens, it should be remembered, were stored under conditions far from "extreme," and for but ten and a quarter months, instead of "from one to two years."

The chemical examination does not show that the solution has any material advantage over chlorinated soda solutions made according to established methods and there is as yet no available evidence that Hyclorite is at all more stable than is any other alkaline solution of hypochlorite.

The findings reported above were sent to the General Laboratories for consideration along with the report of the Council on Pharmacy and Chemistry which questioned various claims made for the product. In reply the General Laboratories admitted that the claims made in regard to the composition of Hyclorite were incorrect: It held that the stability of Hyclorite was greater than that shown by the experiments of the Laboratory, but presented no evidence to substantiate this claim.

Details of Analysis

Hyclorite (Hyclarite) as received was a faintly turbid solution with the characteristic, chlorin-like odor of hypochlorites.

Hypochlorites.—Combined hypochlorous acid was determined by the method described in the U. S. Pharmacopeia VIII, and the findings calculated to "available chlorin." Twenty-five c.c. of the solution were diluted to 250 c.c. and aliquot portions taken for the titration. Twenty-five c.c. of the diluted solution, representing 2.5 c.c. of the original material required, 24.97 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.514 gm. of "available chlorin" per 100 c.c. A duplicate required 25.18 c.c. of the sodium thiosulphate solution, equivalent to 3.543 gm. of "available chlorin," per 100 c.c. A third portion of 25 c.c. required 25.08 c.c. of the thiosulphate solution, equivalent to 3.529 gm. of "available chlorin." Average, 3.529 gm. of "available chlorin" per 100 c.c., or about 3.31 per cent. This is equivalent to about 3.70 per cent. of sodium hypochlorite.

Total Chlorin.—Total chlorin was determined by adding ammonia water to the diluted solution, evaporating to convert the hypochlorite into chlorid, and weighing as silver chlorid in the usual way. Ten c.c. of the original material were diluted to 250 c.c. and aliquot portions were taken for the determination. From 25 c.c. of the diluted solution, representing 1 c.c. of the original material, 0.1908 gm. of silver chlorid was obtained. A duplicate gave 0.1888 gm. of silver chlorid. Average, 0.1898 gm. of silver chlorid, equivalent to 4.69 gm. of total chlorin per 100 c.c., or 4.40 per cent.

Sodium Chlorid.—By calculation it is found that the sodium hypochlorite present (3.94 gm. per 100 c.c.) contains 1.769 gm. of chlorin per 100 c.c.

4.69 gm. of Cl — 1.769 gm. of Cl = 2.92 gm. of Cl, probably combined as NaCl.
2.92 gm. of Cl = 4.818 gm. of NaCl per 100 c.c., or 4.52 per cent.

After being stored for about 10¼ months as described elsewhere in this report the several subdivided portions were assayed for their "available chlorin" content by the method previously used. In some cases 5 c.c. of the solution were diluted to 100 c.c. and in others 25 c.c. were diluted to 250 c.c. Aliquot portions of the dilution were then taken for the assay.

Results.—Original container. Twenty-five c.c. of the dilution, representing 1.25 c.c. of the original material, required 11.35 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.19 gm. of "available chlorin" per 100 c.c., or 3 per cent. A duplicate gave the same results. Flint glass container: Twenty-five c.c. of the dilution, representing 2.5 c.c. of the original material, required 21.52 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.03 gm. of "available chlorin" per 100 c.c. or 2.84 per cent.; a duplicate gave the same result. Amber glass container: Twenty-five c.c. of the diluted solution, representing 2.5 c.c. of the original material, required 21.48 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.02 gm. of "available chlorin" per 100 c.c., or 2.82 per cent. A duplicate gave the same result. Previously unopened original container: Twenty-five c.c. of the solution, representing 2.5 c.c. of the original material, required 21.39 c.c. of tenth-normal sodium thiosulphate, equivalent to 3.01 gm. of "available chlorin" per 100 c.c., or 2.82 per cent. A duplicate gave the same result.

SOFOS

Examination of an Effervescing Sodium Phosphate.

Among the recent patents granted for medicaments, is one for an effervescent form of sodium phosphate. This preparation is now being marketed by the General Chemical Co., of New York, under the name "Sofos." The following statement appears on the label:

"SOFOS is a preparation of mono-sodium phosphate and sodium bi-carbonate. It contains no tartaric or no citric acid. On adding water it effervesces and forms sodium phosphate (di-sodium phosphate). One part of SOFOS has the same phosphate value as 1¾ parts sodium phosphate of the U. S. Pharmacopeia."

The manufacturer claims that Sofos is a mixture of sodium acid phosphate (protected with a thin mechanical covering of disodium phosphate) and sodium bicarbonate, in such proportions that when water is added, disodium phosphate should be formed with the attendant liberation of carbon dioxid.

$$NaH_2PO_4 + NaHCO_3 \rightarrow Na_2HPO_4 + H_2O + CO_2.$$

The Council on Pharmacy and Chemistry, having been requested to recognize Sofos, submitted specimen to the Chemical Laboratory in order that the statements of composition might be checked.

Qualitative tests showed the presence of sodium, very small traces of calcium and potassium, phosphate and carbonate.

If a specimen is treated with water, and then after complete reaction, it is divided in two portions, to one portion sodium bicarbonate is added, more effervescence will take place; if to the other portion, hydrochloric acid is added, effervescence will also take place. This indicates a reversible reaction, depending on the relative concentration of $H^+ + \overline{OH}$, as influenced by the reacting products

$$NaH_2PO_4 + NaHCO_3 \rightleftarrows Na_2HPO_4 + H_2CO_3 \rightleftarrows H_2O + CO_2$$

To test this, CO_2 determinations were made by allowing the mixture to react with water in a Knorr apparatus and aspirating the CO_2 over with air. After this operation, hydrochloric acid was added to the mixture, and the CO_2 thus liberated was also determined. The result shows that 50 to 75 per cent. of the total carbon dioxid (present as carbonate or bicarbonate) could be liberated by the action of water alone, depending on the conditions, i. e., temperature.

Quantitative determinations yielded the following:

Sodium (Na^+)	23.87 per cent.
Carbonate (CO_3^{--})	26.03 per cent.
Phosphate (PO_4^{---})	50.00 per cent.

The amount of sodium based on the phosphate determination by calculating it as being in the form of Na_2HPO_4 (after reaction) is equivalent to 24.20 per cent.; found 23.87 per cent.

The percentage of PO_4 in sodium phosphate U. S. P. is 26.5. Therefore the claim that one part Sofos has the same phosphate value as 1¾ part of sodium phosphate U. S. P. is substantially correct.

Experiment with Human Gastric Juice

1.5041 gm. of Sofos was placed in a Knorr apparatus, and 25 c.c. of water were added. The carbon dioxid was aspirated over by air (a very fine stream of carbon dioxid free air passing through the solution). By the action of water, 71 per cent. of the carbon dioxid was liberated. Twenty-five c.c. of human gastric juice* were then added, and the same operation as above carried out. This raised the percentage of carbon dioxid liberated to 93 per cent. Twenty c.c. more of gastric juice were added, which increased the amount of carbon dioxid liberated to 98 per cent. After these determinations 10 c.c. of normal hydrochloric acid were added, which, after the same operation as the others, increased the amount of carbon dioxid liberated to 99.1 per cent. The total amount liberated, after heating this final mixture was taken as 100 per cent.

From the above, it would appear that the stomach would contain the following after swallowing a dose of Sofos: Disodium phosphate, sodium acid phosphate and sodium chlorid.

AN UNNAMED SYPHILIS REMEDY

An inquiry was received from a correspondent concerning an unnamed remedy for syphilis, reading in part as follows:

"Enclosed please find a capsule which I am sending you for a chemical analysis. These capsules are being sold to the laity at $5.00 each by a man in the liquor business. They are sold as a sure cure for syphilis. Five of these capsules are to be taken in each course and three to five courses are required to cure the disease. They are being sold by Mr. Joe B. Fayant of Golconda, Idaho, who offers a reward of $1,000.00 if anyone can prove that there is any mercury in the capsule."

The claims made for the preparation as reported by the correspondent appeared to be similar to those made for another luetic remedy previously examined. The appearance of the newly received preparation was similar to the older one. Therefore it was considered worth while to make a preliminary examination of the product.

A single capsule was received which weighed approximately 1 gm. The capsule contained a brown mass which had a strong odor of licorice. On being placed in water the mass disintegrated rapidly and the aqueous filtrate obtained from

* This was furnished through the courtesy of Prof. A. J. Carlson. The acidity of this specimen was not determined, but this individual's juice assays close to 0.5 per cent. of hydrochloric acid.

the disintegrated mixture contained copper-reducing substances and sulphates. The insoluble mass consisted of a complex mixture in which a heavy yellow powder, a heavy gray powder and a lighter yellowish gray powder could be detected by the naked eye. By means of the microscope, powdered licorice, starch and finely divided metallic mercury were identified. On treatment with diluted hydrochloric acid the water-insoluble portion effervesced briskly and the heavy, yellow powder went into solution. The filtrate from the mixture gave tests for calcium, for mercury and for a sulphate. The mercuric salt is probably mercuric subsulphate and is present in considerable amounts. The element mercury was also present in considerable quantities. No quantitative determinations were made but from the preliminary tests it seems probable that the preparation has approximately the same composition as the Fisher Remedy for syphilis which was discussed in the Laboratory Report of the American Medical Association, 1915, viii, p. 98.

INDEX

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